Forum

Time Limitation and the Role of Research in the Worldwide Attempt To Eradicate Malaria

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ABSTRACT The U.S. Congress established an intense, time-limited, worldwide malaria eradication program in 1958 and assigned operational responsibility to the U.S. Agency for International Development (and its predecessors). When the program was terminated on schedule in 1963, ~$400 million had been consumed and malaria prevalence had greatly been reduced. Transmission began to increase thereafter. The open-ended WHO global eradication effort began in 1955 ended in 1969 and consumed ~$15 million during the 1958–1963 period of progress, mainly provided by the United States. Intensified anti-malaria interventions continued after Congress discontinued direct support. Although malariological research was discouraged during the period of time limitation, it was embraced as the conceptual basis for the open-ended period of intervention that followed. This effort saved many lives but expended our ability to intervene against future epidemics and reduced human herd immunity. To avoid the "great gamble" inherent in any ambitious intervention against this disease, future programs should be designed to seek incremental, local antimalaria gains.

KEY WORDS malaria, research, health

Soon after malaria was reduced to its global nadir in 1963, Clay Huff summarized his presidential address to the American Society of Tropical Medicine with the words, "... the promise to rid the world of malaria quickly if enough money were available was somewhat like Russian roulette. The game was great; the possibility of failure was underestimated ..." (Huff 1964). The program that he described had largely been created in 1957 by the Congress of the United States and was endorsed by a succession of U.S. presidents—Eisenhower, Kennedy, and Johnson—and was assisted by various United Nations agencies, mainly the Pan American Health Organization (PAHO, then known as PASB), the World Health Organization (WHO), and the United Nations Children's Fund (UNICEF).

Health authorities naturally favor eradication over lesser modes of intervention against infections that threaten their constituencies. John Karefa-Smart, the Minister of External Affairs of Sierra Leone and the former WHO West African Area Medical Officer, illustrated this tendency in his well-received keynote address to a distinguished medical audience that included George Macdonald and Thomas H. Weller. One of us (A.S.) was also present. Karefa-Smart spoke at the height of the global malaria eradication effort, and his remarks were designed to demonstrate that "Eradication is the logical goal of every public health effort directed against infectious diseases ..." (Karefa-Smart 1963). Although the physician must render his patients pathogen-free as rapidly as possible, the public health practitioner must "first" prevent epidemics. This natural attitudinal dichotomy constitutes a proper conflict between medicine and public health.

The extraordinary effort required by an eradication campaign is said to be "intensified" in that the required resources exceed those of the local economies. Because external sources inevitably become exhausted, intensified efforts must be limited in time. Attempts to suppress malaria are particularly time-limited because the anopheline vector tends progressively to resist insecticides, the pathogen loses susceptibility to drugs, financial appropriations become exhausted, herd immunity declines, the operational staff becomes demoralized, and the subject population loses interest in the effort while learning to expect a relatively disease-free state. For these reasons, any heavily intensified antimalaria program (or an intervention against any other vector-borne infection) must be scheduled to deintensify.

The intervention technologies that support a malaria eradication campaign must be fully developed and available for use before operations begin, precisely because the time-horizon is...
short. Professional training, too, must be complete because the program aims also toward the extinction of malariologists; they should soon have little to study (Gramiccia & Beales 1988). Basic research and high-level training had no place in the great gamble that Huff described. Such advocacy would be subversive.

Time-limitation and a rejection of research appropriately distinguished the highly intense phase of the worldwide malaria eradication program from other, less-structured efforts. The discussion that follows analyzes the long-term consequences of this discontinued effort. In particular, we shall identify the conceptual origins of the promise to eradicate malaria, contrast the components of bilateral and multilateral efforts, follow the line of reasoning that permitted the interlaced tactics to remain in effect, and describe how research attitudes shifted as the prevalence of malaria began its present ascent toward another zenith.

**Early History of Eradication Efforts**

Realistic attempts at disease eradication trace back to the establishment of the Bureau of Animal Industry in 1884, for the suppression and extirpation of contagious disease among domestic animals and its attempts to eradicate animal tuberculosis in 1888 and 1892, when the secretary of agriculture proclaimed the United States free of bovine contagious pleuropneumonia (Hagen 1922).

Eradication efforts directed toward agricultural pests similarly date to this period. The deliberate introduction into California, for example, of an Australian lady bird beetle greatly reduced the damage caused by the cottony cushion scale, itself an invader from that continent.

In the case of human disease, an early discussion of eradication analyzes Gorgas’ work on yellow fever in Havana in 1901, the Rockefeller Foundation sanitary commission for the eradication of hookworm disease in 1910 and yellow fever in 1915: “Preliminary arrangements have been made for a survey to determine the feasibility of undertaking at this time the eradication of yellow fever, and for experiments to test the practicability of controlling malaria.” (Rockefeller Foundation 1915). Thus, following the disappearance of yellow fever from Cuba and Panama, global eradication was considered; but for malaria, less-ambitious goals were then specified.

The earliest detailed argument for the eradication of malaria seems to have been expressed by an insurance actuary who presented an eloquent plea for a national committee on the eradication of malaria and a well-reasoned plan for implementing that goal (Hoffman 1917).

“The period between the late 1920s and the early 1930s was probably this century’s low point in acceptance of the eradication concept in the prevention of communicable diseases.” (Soper 1965). This in part was related to the emergence of jungle yellow fever and a transient outbreak of this infection that struck Brazil.

The concept of eradication began to regain favor when the Mediterranean fruit fly was eliminated from Florida (1930–1931) and with F. L. Soper’s remarkable *Anopheles gambiae* eradication campaign in Brazil (1934–1940). This antimalaria effort was based on a comprehensive understanding of the ecology of the target insect, considered factors such as topography, terrain and drainage systems, included an excellent surveillance system and rested on a varied armamentarium of intervention (Soper & Wilson 1943). Although the sponsoring agency, the Rockefeller Foundation, appeared to avoid the term “eradication” in this first *An. gambiae* campaign, its success was largely responsible for the rehabilitation of the eradication concept.

This victory was followed by a campaign against a wartime introduction of *An. gambiae* in Upper Egypt, and by the program to eradicate *Ae. aegypti* from Brazil (1942) and the Americas as a whole (1947). A final attempt to apply the concept of species eradication to malaria was directed against *An. labranchiae* in Sardinia in 1946–1950 (Logan 1953, Kitron & Spielman 1989).

Initially, vector eradication seemed practical where infection had recently been introduced, or in island or other “limited geographical units where infection had been eradicated and with some natural protection against reinfection” (Soper 1948). Eradication was considered feasible if the public health burden of the relevant disease exceeds the cost of eradication, if the vector is vulnerable to attack in one or more of its life stages, if the vector can be eliminated incrementally from limited portions of its range, if natural barriers protect cleared regions from reinfection, if necessary funding, labor, and authority are available, and if the presence of the vector can effectively be monitored. “As long as evidence for the existence of the [vector] species continues to appear, the campaign has been a failure. There is no such thing as partial success in species eradication; one either achieves glorious success or dismal failure” (Soper 1948). The Sardinia experiment would seem to fit into the latter category.

A conceptual prelude to the intensified worldwide eradication effort was launched in the United States during World War II, soon after DDT became available for antimalaria interventions. In 1943, L. L. Williams proposed that the U.S. Public Health Service (USPHS) “sponsor and coordinate a program for malaria eradication to be executed through state and local health departments, and that the Congress be requested...
to make an appropriation . . . .” Mountin (1944) presented this program to the National Malaria Committee, describing the status of malaria in the United States and the logic of intervention. He emphasized that vector Anopheles need not be eliminated and described a variety of suppression measures that emphasized the role of the USPHS. A congressional appropriation for malaria “eradication” was requested, but secured as an “Extended Malaria Control Program,” because of opposition to the term eradication (Williams 1945). The effort was funded in 1947.

The Extended Malaria Control Program “represented a complete change from previous malaria control activities. Larvicides, drainage, and programs to promote insect-proofing of houses were abandoned and efforts were concentrated upon the use of indoor residual DDT sprays . . .” (Andrews et al. 1950). The concept was to target only the potentially infectious portion of the vector population and to concentrate on selected regions. In 1947, this principle was extended to the entire southeastern quadrant of the United States. Hundreds of USPHS jobs and a large reservoir of personal pride were involved (A. D. Langmuir, personal communication). Interestingly, Alexander Langmuir, who directed this $7 million program for the USPHS, terminated the effort when he discovered that no U.S. cases of malaria clustered in place and time even before this program began. Malaria had already been eradicated.

Rationale Behind the Intensified Malaria Eradication Campaign

The availability of DDT combined with the then emergent understanding of the dynamics of malaria transmission during the 1950s to provide impetus for the eradication concept. George Macdonald, of the Ross Institute in London, constructed a model of transmission in 1956 based on Ronald Ross’s original mathematical constructs. He formalized the eradication concept by demonstrating that the weak link in the transmission cycle of malaria lies in the survival of the adult vector relative to the extrinsic incubation period of the pathogen. The cycle could most readily be broken by increasing mortality among the potentially infectious members of the vector population; that is, those mosquitoes that had fed on people. Accordingly, domestic applications of residual insecticide, sprayed around human sleeping quarters, emerged as the single most effective intervention tactic. Intervention coverage could be measured in terms of the proportion of houses treated rather than of their more vagile inhabitants. DDT was the ideal insecticide.

The element of urgency in the eradication effort derived from the belief that agricultural as well as public health use of insecticide leads inevitably to insecticide resistance in vector insects. The power of DDT stimulated enormous optimism, coupled with a growing anxiety that this power might become lost. Medical entomologists “believed in DDT” and looked toward the obsolescence of their discipline. Resistance generally seemed to develop between 5 and 10 yr after the use of an insecticide was intensified against a particular target. The usefulness of DDT, therefore, was recognized as temporary.

This conjunction of events coincided with the developing career of an extraordinary public health administrator, Fred L. Soper, who enjoyed a long history of successful health interventions. As an officer of the Rockefeller Foundation, he led the campaigns that eliminated An. gambiae from Brazil and Aedes aegypti from much of Latin America, among other accomplishments. He took a leading role in the formation of the Pan American Sanitary Bureau (later to become PAHO) and to structure that agency so that it was independent of WHO. His vision of a disease-free future was readily embraced by other physicians and politicians and matched the mood of optimism that dominated the thinking of the time. Soper’s immense persuasive and administrative powers provided the catalyst that energized the antimalaria program. Interestingly, his published memoirs contain no reference to this monumental effort (Soper 1977).

Soper’s long-term associate at the Rockefeller Foundation, Paul F. Russell, provided the scientific basis for the eradication concept. Russell’s optimism matched that of Soper, and his gentle manner complemented Soper’s harsh style. His contemporary treatise “Man’s mastery of malaria” eloquently testifies to his own conviction that malaria eradication was then “within man’s grasp.”

“Only in recent years, with the development of the Pan American Health Organization, the World Health Organization, the Food and Agriculture Organization of the United Nations, the International Cooperation Administration of the U.S. and UNICEF has there existed adequate mechanism for coordinating and assisting regional and world eradication programs.” (Soper 1958). An administrative basis for the intensified malaria eradication program was in place.

In this manner, global malaria eradication derived from a unique combination of circumstances that included: a growing appreciation of the epidemiological importance of vector longevity, the availability of DDT, an awareness of the dangers of insecticide and drug resistance, the global domination by the United States, the emergence of United Nations-based multilateral bodies, the personalities of F. L. Soper and P. F. Russell, and a general optimism pointing toward a better world to come.
Multilateral Efforts

International travel and communication greatly increased in the mid-twentieth century, thereby facilitating importation of malaria while fostering international cooperation in its suppression. “The countries of the Americas have, for the first time in the PASO, a convenient framework through which the effective teaming so vital to eradication campaigns can be carried out, …” (Soper 1958). “Once the concept of malaria eradication was accepted, PAHO, WHO, UNICEF, and ICA, all became vitally interested in the careful planning, meticulous administration, complete coverage, continuing evaluation and coordination of malaria prevention in contiguous areas across international frontiers required for the success of each national eradication program.” (Anonymous 1961).

The Eighth World Health Assembly, therefore, recommended in 1955 a program of time-limited eradication of malaria out of concern for “the danger constituted by the potential development of anopheline resistance to insecticides….” The Assembly expressed “the fear [that] has arisen that the permanent maintenance of control by means of the residual insecticides might prove impossible owing to the growth of anopheline resistance to them.” (Anonymous 1963). The Assembly “Request[ed] governments to intensify plans of nation-wide malaria control so that malaria eradication may be achieved and the regular insecticide-spraying campaigns safely terminated before the potential danger of a development of resistance to insecticides in anopheline vectors materializes; … [and] Decide[d] that the World Health Organization should take the initiative, provide technical advice, and encourage research and co-ordination of resources in the implementation of a programme having as its ultimate objective the world-wide eradication of malaria….” The development of insecticide resistance among vector anophelines created the atmosphere of urgency “that was largely responsible for the adoption by the … Assembly of the policy of malaria eradication” (WHO 1958). A Malaria Eradication Special Account was established in addition to the regular budget of WHO for the purpose of receiving “voluntary contributions” to be used in funding this operational effort as well as an unspecified program of research.

Although the Assembly specified no firm date for terminating the eradication effort, WHO recognized that time-limited intensification was essential to eradication: “Malaria eradication means the ending of transmission of malaria and the elimination of the reservoir of infective cases in a campaign limited in time and carried to such a degree of perfection that, when it comes to an end, there is no resumption of transmission.” (Anonymous 1957). “Eradication campaigns are characterized by time limits.” “An eradication programme must be looked on in its entirety: adequate and continued financial provision for the whole is a necessity….” Original estimates should therefore include a statement of the whole programme, and its costs, from start to finish. Approval should be sought for the whole.” (Anonymous 1963).

The duration of an eradication effort was a subject of discussion. “An eradication programme in an area where transmission had not previously [sic] been interrupted might require four or even five years of [indoor residual] spraying. If in this area malaria control had already interrupted transmission, then the eradication might require only three or four years of spraying and the control programme could certainly be referred to as a step towards an eradication campaign.” (Anonymous 1963). Venezuelan experience had suggested that a 5-yr span might be reasonable: “Depending upon the nature of the vector, malaria can be eradicated in 3–5 years. In the case of certain outdoor-biting vectors, however, eradication may not readily occur.” (Gabaldon 1956). This suggestion of potentially open-ended intervention activity became a focus of controversy.

Somewhat contradictory, however, were the practical operational guidelines specifying that withdrawal of spraying is “permitted” in India when the annual parasite index (API) (which describes incidence of malaria diagnoses based on a passive surveillance system) is 0.5 per thousand in hyperendemic regions and 0.1 where infection is endemic. In Ceylon, the maximum permissible incidence was 0.05 and in Indonesia it was 0.1 (Anonymous 1963). These specifications permitted eradication efforts to be discontinued before the infection disappeared. In effect, the WHO effort was open-ended.

U.S. Congressional Action

The tightly reasoned IDAB Report (International Development Advisory Board) set the basic terms for subsequent U.S. action on malaria eradication (Anonymous 1956a). Wilton L. Halverson chaired the committee and Paul F. Russell served as its special consultant. After discussing the exceedingly useful antimalaria properties of indoor residual applications of DDT, the report reasoned that “Generally, it takes four years of spraying and four years of surveillance to make sure of three consecutive years of no mosquito transmission in an area. After that, normal health department activities can be depended upon to deal with occasional introduced cases….” [Therefore] Eradication can be pushed through in a community in a period of 8–10 years, with not more than four to six years of actual spraying, without much danger of resistance. But if countries, due to lack of funds, have to proceed slowly, resistance is almost cer-
tain to appear and eradication will become economically impossible. \textit{Time is of the essence} because DDT resistance has appeared in 6 or 7 years. ... This is a completely unique moment in the history of man’s attack on one of his oldest and most powerful disease enemies. Failure to proceed energetically might postpone malaria eradication indefinitely. The Committee finds that today the eradication of malaria is technically practicable in most parts of the world, ... and unless this unique opportunity is exploited without delay, it may be lost due to development of resistance by mosquitoes to the insecticides that make eradication technically and economically possible now.”

The U.S. World-Wide Malaria Eradication Program commenced in 1958 at the height of the Cold War, in the wake of Sputnik, and during a period in which the unprecedented wealth of the United States permitted it to lead in world affairs. Congress funded the program. Two powerful senators—Hubert H. Humphrey and John F. Kennedy—sponsored the enabling legislation for malaria eradication under the Mutual Security Act. This act derived from the IIAA, Marshall Plan for Europe (1948), and the Point IV Program (1949), which later was to become embodied in the ICA and U.S. Agency for International Development (AID).

It was argued that malaria-endemic countries would benefit economically from a successful eradication campaign. Improvements in health for residents of foreign lands would also translate into savings for U.S. consumers of imported products. Indeed, the burden of malaria “among laborers overseas who produce the goods purchased by the United States requires on the average at least 5 percent of the annual production budgets. This constitutes a hidden malaria tax of more than one-third billion dollars paid annually by the United States on its imports.” (Ibid). Thus, an anticipated long-term gain to the U.S. economy provided a crucial argument in favor of eradication.

Interestingly, malaria eradication was authorized in the legislation that provided appropriations for many of the main military alliances of the United States. An annual appropriation of $23.3 million was provided for malaria-related activities, an enormous investment for the time. The appropriation was to be repeated over a 5-yr period but was not to be renewed beyond the stipulated closing date in 1963. This investment was intended to produce an endpoint that was undeniably irreversible zero prevalence of malaria.

This congressional action was offered in the context of a speech delivered by President Dwight D. Eisenhower in which he “declared total war, not upon any human enemy, but upon the brute forces of poverty and need.” A “war metaphor, with its unstated hope that there will be victory for our side, also prepares us poorly for the long-term consequences of [a persisting disease]. Wars eventually end [and are] followed by a time of peace.” (Kenniston 1989). Paraphrasing Russell (but without citation), Eisenhower elaborated on this concept of “unconditional surrender” by stating, “We now have it within our power to eradicate from the face of the earth that age-old scourge of mankind: malaria. We are embarking with other nations in an all-out five-year campaign to blot out this curse forever.” (Quoted in Soper 1958). “No other international health program has received such strong and consistent support at the very highest levels.” (From a recorded speech by C. L. Williams, 20 September 1966). President John F. Kennedy reiterated this support.

His successor, Lyndon B. Johnson, in his State of the Union message in 1964, said, “Both of my predecessors committed the United States to [malaria eradication]. ... The Congress has endorsed this objective and has supported it financially. We will continue to encourage WHO in its work to eradicate malaria throughout the world and will continue to aid friendly nations toward this objective.” (Quoted by C. L. Williams in a recorded speech, 20 September 1966). Interestingly, these words subordinated the antimalaria role of the United States, for the first time, to that of WHO. President Johnson’s next recorded comment rendered its role still more ambiguous by equating the U.S. antimalaria efforts with that against a disease for which no intervention program existed. He stated on 9 August 1965, “The American goal is to eradicate malaria and cholera from the world.” (Quoted by C. L. Williams in a recorded speech, 20 September 1966).

Paradoxically, the infectious enemy was to be engaged in a campaign that ignored difficult battlegrounds. Representing the ICA before the Senate Appropriations Committee, C. L. Williams (1957) testified that “Within certain technical limitations ... [the eradication of malaria] ... is possible through the use of tried methods, personnel, equipment, and supplies which are now available or could be made available. The only exceptions to this conclusion are certain areas of the world known or suspected to harbor malaria which are relatively inaccessible. ... The situation in tropical Africa is such that eradication cannot be visualized in the immediate future. ... No doubt malaria can and will be eradicated in these areas in due time.” Thus, while the eradication campaign proceeded elsewhere in earnest and with pressure to succeed within a defined period, tropical Africa as well as other “inaccessible” areas were to be considered at some future date. Consideration of the threat of outbreaks due to human migration and the movements of mosquitoes from such sites was postponed.
The "Mutual Security Act in 1958 contained specific authorization for malaria eradication as a line item in the budget. Unfortunately, it was eliminated after 1961, the last year in which it appeared [phased out entirely by thirds from 1961 to 1963]. From that time forward, we have had the problem of competing for malaria eradication funds at the country programming level. We are hoping that we can change it back again, but at the moment we can report little progress." (from a recorded speech by C. L. Williams, 20 September 1966).

The scheduled conclusion of U.S. congressional funding in 1963 transformed the various existing malaria eradication efforts. The original logic behind intensification for both agencies revolved around the anticipated loss of effectiveness of DDT as well as other residual insecticides, and that potential became increasingly manifest as a crucial operational obstacle. Smaller was convinced that the cycle of transmission of malaria could be broken everywhere except in Africa within a 3-yr period of time. The eradication schedule presented to Congress stipulated a 5-yr effort in order to include a 2-yr period in which residual problems could be eliminated.

The subsequent 1960 ICA Expert Panel on Malaria recognized that the 1957 IDAB projection of a 3- or 5-yr terminal date for eradication was overly optimistic. Instead, 8 yr seemed more reasonable; but even that might not be realistic in certain situations. The cost of worldwide eradication was revised upward >10-fold to a total of $1.3 billion, of which $390 million must be supplied externally. By 1966, the director of the AID program (C. L. Williams) stated, "We have already spent several times the [projected amount], and the end is still not in sight. . . . The U.S. contribution has been very, very substantial indeed." (from a recorded speech by C. L. Williams, 20 September 1966).

In the course of transferring responsibility for the conduct of eradication to the Centers for Disease Control (CDC), Williams addressed the issue of time-limitation by saying, "We perhaps gave a misleading impression when we led many people to believe that we were going to be successful in the eradication of malaria within 5 years. I am inclined to feel that this was an error of interpretation. I don't believe if you look back at all of the careful statements that we wrote, the testimony that we prepared for Congress and so on, I don't believe that we ever made such a commitment. We clearly left that impression, whether we intended to do it or not. And from time to time we have gotten back from the financial officers of AID, from congressmen and even from the White House, questions [such as], 'Well, you said that you were going to do this in 5 years and it has now been 9 years; How come? Is the end in sight? How long is it going to be?'

The statement that I remember that we made was that malaria eradication is technically feasible within 5 years." (quoted from a recorded speech by C. F. Williams, 20 September 1966). The Congressional Record indeed includes such a statement, but the distinction seems excessively fine.

On 3 March 1966, an interagency agreement was signed transferring to the Public Health Service the responsibility for the operational phases of the malaria eradication campaign. CDC personnel thenceforth represented the U.S. government in place of AID. The first such interchange was a meeting with WHO representatives in Atlanta on 22 October 1966.

**Funding**

The IDAB report estimated that in "1956 a total of about $56 million would be spent for malaria . . . in the world, $44 million by national governments, $8 million by international agencies, and $12 million by direct I.C.A. assistance" (Anonymous 1956b). It estimated that "widespread malaria eradication . . . could be carried out for a five year (1957-61) total of about $519 million. . . . Of this amount, the national governments concerned might appropriate some $330 million and international agencies some $50 million, leaving a balance of $139 million required from other sources. I.C.A. could provide this, by increasing its expenditures to $28 million per year." ICA then was assisting 21 countries in malaria control in 1956 at a cost of >$12 million.

In 1956, before the intensified program began, ICA also provided 57.5% of the UNICEF budget and 50% of the United Nations Technical Assistance (UNTA) budget. Some $689,000 of WHO and UNTA money was to be spent on eradication in 1956. Interestingly, the WHO Special Account for Malaria Eradication included in 1956 only $9,900 from Brunei, $4,000 from Taiwan, and $48,000 from the Federal Republic of Germany. PASO was to spend $193,000 in 1956. UNICEF was to supply >$7 million in commodities.

The enabling U.S. congressional action estimated that the 5-yr worldwide Malaria Eradication Program would cost $515 million, of which the United States would provide $108 million and the various multilateral agencies would pay $42 million. The annual appropriation would be $25.5 million of which $5 million would go to WHO and $2 million to the Pan American Sanitary Organization. "The program in brief: The following is a proposal that the United States Government through the International Cooperation Administration, participate in a 5-year world-wide program to eradicate malaria in collaboration with the nations of the free world and the World Health Organization, the Pan American Sanitary Organization, and the United Nations Children's Fund." The United States was
WHO Regular Budget appropriation remained the pitifully small; by the United States. WHO, therefore, to assist those nations in appropriation of $5 million. The PASO share of the objective of intensifying the ongoing antimalaria efforts of the "60 nations of the free world" and thereby raise total attendant antimalaria expenditures from $44 million to $61 million. Other nations, where no bilateral U.S. programs were in effect, would be served by the WHO appropriation of $5 million. The PASO share of this multilateral assistance would be the designated $2 million in addition to a $4 million appropriation that would underwrite the various Central and South American nations' own share of the antimalaria effort. In contrast, some $60 million had been devoted to bilateral antimalaria programs during the preceding 15 yr. The role of WHO, therefore, was to assist those nations in which U.S. agencies could not operate.

Actual AID expenditures between 1958 and 1963 totaled $230 million in hard currency plus $200 million in local currencies (provided under Public Law 480). The United States contributed 31.2% of the WHO overall budget, 66% of that of PAHO and 40% of that of UNICEF (including $6.5–7 million for malaria eradication). Gramiccia & Beales (1988) estimated that WHO spent only $15,205,969 on antimalaria activities during this period, of which $15,500,000 were donated by the United States.

The annual budgets of the Pan American and World Health Organizations were pitifully small; only as the United Nations Children’s Fund (UNICEF) became interested and as Technical Assistance funds became available through the United Nations could these health organizations undertake active collaboration in malaria control.” (Anonymous 1961).

The availability of U.S. funding transformed the already-existing WHO eradication program. At the height of the campaign, the U.S. congressional appropriation amounted to >95% of the WHO eradication budget (WHO 1959). The Malaria Eradication Special Account rose from $36,600 in 1957 to $51.1 million in 1958. The WHO Regular Budget appropriation remained relatively constant at about $0.7 million and the Expanded Programme sum rose from $0.6 million to $0.9 million. This level of funding continued until 1963, when the U.S. congressional contribution was phased out. In anticipation of the impending budgetary crisis in the special fund, the Thirteenth World Health Assembly decided “that the administrative and operational services of the malaria eradication programme shall be financed from the supplementary budget” of the WHO (WHO 1962). Some $2 million was to be transferred to this account in 1963 and $4 million in 1964. Thereafter, the full $6 million required for the special account was to be derived from central WHO funding. This use of central funds permitted an element of multilateral support for intensified spraying to be continued essentially without limit of time.

A definitive General Accounting Office report (Anonymous 1982) estimated that the total U.S. antimalaria expenditure exceeded $989 million for the period between 1950 and 1981, with $677.3 million going to bilateral programs, $131.0 million to multilateral programs (including $89 million to the general operating budgets and $42 million to special eradication accounts), and $181.2 million in research and development ($179 million directly and $2 million through the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). Some $114.7 million was spent before the United States entered the mode of eradication and $407 million between 1957 and 1969.

Sequelae

Long after malaria eradication was formally abandoned as a global objective, basic features of the original eradication strategy remained in effect. The showcase eradication effort of Sri Lanka, for example, was converted on 6 May 1977 into “an intensive malaria control programme” that was mainly supported by USAID and advised by WHO (A.S., unpublished data). Its “attack phase” commenced in 1968 in the face of a longstanding epidemic and in response to an ambitious economic development plan. “The goal of the original AID plan of operations was stated in 1977... The specific technical malaria control objectives to be reached during this period are to reduce malaria to less than... one case per 1,000 population and to eliminate P. falciparum infections... In 1979, the goal was modified... The specific technical objectives to be reached during this period are to reduce malaria to less than... one case per 1,000 population (sic)... The 1977 document described the project as ‘a large scale five-year effort’... But in 1979, the description specified only that the project was ‘a large scale effort.’ Both documents specified that... The primary reason for a largescale and intensive malaria control program in Sri Lanka is to control malaria before this vector develops resistance to malathion... Surveillance is to provide the basis for terminating the intensified effort, and the 1977 document includes a detailed description of case detection methodology. No discussion of mechanism of withdrawal is included in the 1979 document.”

The plan of operations of WHO, which continued unmodified into the 1980’s, corresponded to the 1977 AID document (A. Noguer, personal communication). “The basic objective of this intensive programme was to eradicate P. falciparum and to reduce the prevalence of P. vivax to an acceptable low level. The epidemiological findings during 1978 to 1981 will be considered
as the basis for reduction or withdrawal of spray operations." Thus, the main sponsoring agency appeared to change the terms of its sponsorship during the course of the program and the main coordinating agency failed to coordinate with this basic change in direction.

These rather inconsistent goals for Sri Lanka were to depend on residual applications of malathion, applied to the exterior as well as interior surfaces of all structures in the endemic region four times during each of the first 2 yr, two times in 1979, and eliminated by 1981 (AID, 1977, unpublished document). The cost of this effort, which was underwritten by the United States, the United Kingdom, and The Netherlands, exceeded the entire nonmalaria health budget of the country. Some 7.5 million pounds of malathion were to be applied each year to protect an exposed population of ~12 million people. The various sponsors continued this level of support for nearly another decade (AID, 1986, unpublished report) even in the face of mounting evidence of drug and insecticide resistance, demoralized spray teams and steadily increasing levels of malaria transmission. The eradication-oriented methodology that was implemented in 1958 remained intact in Sri Lanka from 1976 until external support waned in the late 1980s; only the program strategy changed to meet the antimalaria philosophies of the moment.

The confusion that surrounded the goals of the Sri Lankan antimalaria program and the problematic criteria for deintensification were reflected in many other programs. These included the "malaria control" efforts proposed for Zanzibar in 1981 (Anonymous 1981) and implemented in Indonesia in 1980 (Johnson & Kesavalu 1987), Pakistan in 1982 (Scholtens et al. 1990), and Ecuador in 1985 (Breeland et al. 1987). The sponsors of these efforts generally resolved the paradox between deintensification and time-limitation by invoking the promise of a vigorous program of research, while suggesting that an endless chain of substitute intervention technologies would soon become available.

Indeed, U.S. funding continued to support intensive antimalaria interventions throughout the 1960s. The quantity of DDT that AID provided to the various country programs serves to mark the degree of "intensification" (Johnson 1973). DDT use for antimalaria purposes was greatest in 1963, when 61 million pounds were purchased (Fig. I). But, even though the congressional appropriation for malaria eradication had expired, DDT use continued almost unabated throughout the decade. Environmental concerns eventually caused the virtual abandonment of this product thereafter. The global eradication effort, in effect, became open-ended. The program continued in clear violation of the logic that governed its inception.
World wide malaria eradication was formally abandoned by the WHO at the World Health Assembly of 1969. The next assembly endorsed this "revised strategy of malaria eradication" and recommended that "malaria control schemes [be organized] within the general health services" of countries where transmission continues and endorsed "intensifying both fundamental and applied research." (Twenty-third World Health Assembly. WHA23.12). "This will necessitate reorientation of the malaria eradication efforts from that of countrywide comprehensive coverage to more limited epidemiologically oriented programs directed toward the containment of malaria—especially in areas of intense transmission." (Scholtens et al. 1972). Intensified suppression had been replaced by an array of reactive containment efforts (Spielman & Rossignol 1984).

A Chronology

The following sequence of events summarizes the events that mark the creation and termination of the global malaria eradication campaign:

1945—UNRRA assists Italy and Greece in malaria eradication.
1944-1945—DDT trials performed in Italy.
1946—Missiroli outlines a plan for the eradication of malaria in Italy.
—Vector eradication is attempted in Sardinia.
—UNRRA proposes malaria control program to WHO Interim Commission.
1947—Commitment of PAS Organization (Pan American Sanitary bureau) to eradication of Ae. aegypti.
1948—Pampana supports malaria eradication as a reasonable goal.
1950—At the 13th Pan American Sanitary Conference (PASC), Soper proposes malaria eradication as an international health program. Pan American Sanitary Bureau (PASB) adopts general principles and "recommends that the PASB stimulate and coordinate anti-malaria programs and arrange economic assistance to individual countries, in order to achieve continental eradication of malaria." (Anonymous 1961)
—13th PASC approves a continental program for smallpox eradication.
—Haiti countrywide anti-yaws campaign is executed.
—13th PASC approved a continental program of yaws eradication.
1951—Emergence of insecticide resistance in anophelines in Greece (Scholtens et al. 1972).
1954—14th PASC declares malaria eradication an emergency need and demands that PASB carry out its 1950 resolution.
1955—Mexico decides to undertake malaria eradication and appeals to UNICEF for assistance.
—UNICEF/WHO Joint Committee on Health Policy approved the inclusion of malaria eradication among supported programs.
—VIII World Health Assembly authorized the WHO to implement "a programme having as its ultimate objective the world-wide eradication of malaria; \ldots\
1956—Decision of U.S. government to sponsor programs of PAHO and WHO. Transformation of all control projects supported by ICA (AID) to eradication campaigns.
—UNICEF declares that it would no longer support malaria control but only eradication.
—IDAB report to ICA recommending conversion of all control programs to eradication programs.
1957—Section 420 of the Mutual Security Act passed.
—Malaria programs administered centrally within ICA and specific budgets submitted to Congress.
1958—U.S. congressional support for malaria eradication commences.
1961—Programs administered by regional bureaus within AID and budgets no longer submitted to Congress. (AID replaces ICA).
1963—U.S. congressional support ends. AID employs 80 technical malaria advisors.
1965—AID requests that the USPHS administer its antimalaria programs.
1966—USPHS assumes responsibility for programs "after AID made a firm commitment to support the then ongoing 15 country programs to completion."
—An agreement was signed on 3 March in which the USPHS agreed to furnish resident advisors; 39 AID direct-hire malaria advisors continuing in the program were transferred to PHS. Policy determination and programming support remained with AID's regional bureaus.
1968—AID notified PHS that antimalaria funding would be reduced (July).
1969—AID multilateralizes. CDC then had 64 Americans working on malaria overseas and 22 in Atlanta.
1970—A memorandum of understanding between AID and USPHS stated that all bilateral technical malaria services would be phased out.
—AID announces that it will assist WHO to assume full responsibility for multilateralization.
1972—PHS notified AID that the memorandum of understanding of August 1970 would be terminated on June 30.
1976—AID Audit Report finds that malaria is heavily resurgent and recommends formation of a new strategy.
1982—GAO reports that $989 million had been spent on a failed program.

The following quotations illustrate the rise and fall of the concept of malaria eradication (see also Kitron 1987):

In Europe, having regard to the present state of knowledge, the correct anti-malaria practice is to endeavor to reduce the incidence and severity of the disease. Measures designed to accomplish more than that (particularly measures aiming at 'eradication') are not a wise proposition and can be justified only in very exceptional circumstances.—(League of Nations Malaria Commission 1927)

The concept of malaria eradication was born in the United States, but its growth was slow. It had to overcome the dictum that while malaria could be controlled, eradication should not be attempted. . . . In 1943 the concept of eradication was accepted, but its terminology was not. Too many years had been spent in emphasizing control in the belief that eradication was unjustified because of the certainty of reinfection.—(Williams 1958)

This will necessitate reorientation of the malaria eradication efforts from that of countrywide comprehensive coverage to more limited epidemiologically oriented programs directed toward the containment of malaria—especially in areas of intense transmission.—(Scholtens et al. 1972)

In many tropical endemic sites, locally controlled integrated malaria management programs may lead to maintainable gradual suppression of transmission of malaria.—(Kitron & Spielman 1989)

Research

Malariological research had no place in the AID eradication effort of 1958–1963. While the operation proceeded in a time-limited eradication mode, any meaningful research program seemed superfluous. Why study something that is about to disappear? Do we lack any necessary techniques? Indeed the original Mutual Security Act contained no research provisions, and the AID administrators of the program in those years deliberately excluded this function. Research advocacy was subversive.

Only a few lamented the demise of malariological research: “. . . there should not have been a de-emphasis of basic research and training in all aspects of malariology including control but that, instead, the efforts towards an accelerated attempt at eradication should have been added to these efforts.” (Huff 1964). Their voices were largely ignored: “However, to voice such doubts has become tantamount to being the devil’s advocate or to being against virtue. To the few voices which have been raised questioning the advisability of using this mass effort as quick and final solution have not been heard in the din of shouting about initial successes.” (Huff 1964).

Interestingly, a $2 million research fund was established by Congress in 1959 for the purpose of developing programs for other diseases. The stated objective was “to determine the feasibility of future intensive programs for reduction, control, or eradication of disease problems of international importance.” (Section VI of Public Law 86-108 of 24 July 1959). These funds, presumably, would not have been appropriate for malariological research.

Organized malariological research programs began to resurface, however, after the time-limited nature of the eradication program had been abandoned in 1963. The new rationale, then, could be paraphrased as “Yes, intensive use of killing chemicals cannot be continued without limit of time because the target population will ultimately adapt. Scientific research efforts, therefore, will be used to provide sustainability. Appropriate funding, deriving from a tax on the operational budget, will provide a contin-
uous series of replacement intervention technologies.” One of the most influential supporters of the eradication concept, George Macdonald, acknowledged in 1965 that malariological research had become appropriate with the words, “Research is needed, although always in parallel to operational schemes. Never, as happened too often in the past, should it consist of preliminary studies which indefinitely delay the start of activity and have no real prospect of solving operational programs. No more preliminary experiments are required... The principle of eradication in contrast with control derives largely from Soper. He has seen the goal of eradication well advanced, and there seems no valid reason why he should not see it reached.” Research had regained legitimacy.

Thereafter, research assumed an increasingly prominent place in the eradication programs of AID and WHO. Indeed, the U.S. Congress began to appropriate funds for biomedical research, especially in developing countries, within five years (Brady in Anonymous 1985). This misguided but enduring optimism by the senior assistant administrator for science and technology of AID is reflected in repeated rounds of requests for proposals for vaccine-development, the most recent carried a deadline of October 1992. A useful immunogen has yet to be developed, in spite of a quarter century of intensive effort. We are still “Waiting for the vaccine” (Targett 1991).

This program of antimalaria vaccine research was directed mainly toward immunogens simulating epitopes on the sporozoite stage of the pathogen, an objective that seems peculiarly inappropriate for use on permanent residents of malarious regions. If such people were to be vaccinated successfully, they would become progressively naive against the stages of the pathogen that more directly cause disease. In the event that protection was less than lifelong (as seems likely), any failure to revaccinate would increase the burden that malaria places on populations. This “visitor’s vaccine” (Clyde 1987) could have no effect on the force of transmission of malaria. Although the effect would be less dramatic, certain disease-modifying vaccines seem more promising (Mendis 1991). Conflict and accusations of dishonesty have surrounded this vaccine program (Marshall 1988).

The focus of research optimism seems to have shifted recently from vaccine development toward molecular entomology (James 1992, Miller 1992). Advocates of these sophisticated research activities promote studies designed to genetically transform vector anophelines such that they cannot support the development of the malaria pathogen. Malaria oocysts would be melanized before sporozoites could develop. Such “designer gene” mosquitoes would then be re-
leased in endemic sites where they would feed harmlessly (?) on people. These beneficial mosquitoes are expected to replace the native vector mosquitoes through some unstated mode. Invading transposable elements may provide a vehicle for such displacement (Kidwell & Ribeiro 1992). But, because no such transposon has been demonstrated in mosquitoes, malariological studies on this possibility are now conducted on fruitflies. Even if such speculative competitive displacement were effective, few knowledgeable residents of malaria-endemic sites would tolerate deliberate infestations of anthropophagous mosquitoes placed near their homes, however "beneficial." Any expectation of widespread altruistic sacrifice in one's own "backyard" seems misplaced. The "cutting edge" of malariological research appears to have turned deep into the laboratory.

A balanced statement of the malariological research problem was presented recently by Bradley (1991). A "great range of imperfect tools for malaria control" already exist, and these can be applied locally, with good effect. He cites Blake's admonition that "He who would do good must do it in minute particulars; the general good is the cry of the charlatan." Incremental local gains are more likely to be sustainable than are general global victories.

Conclusions

Huff's "great gamble" shadows any intensified program directed against a vector-borne infection. "Untimely proposals for eradication of such diseases as ... onchocerciasis [or of guinea worm] ... can only lead to disappointments. . . ." (Jeffery 1976). The consequences of failure require careful consideration.

Although support for world-wide malaria eradication was discontinued by the U.S. Congress as scheduled, in 1963, its short-term accomplishments contained many of the elements of a major victory (Johnson 1973). Health had improved greatly; many millions of malaria infections had been prevented and uncounted lives saved. Intolerable human suffering would have followed any cessation of antimalaria activities. It became unarguable that antimalaria activities must be continued; the then nonimmune residents of these regions could not have been abandoned to malaria's inevitable return. The admirable logic that ruled the original 1955-1963 intervention, however, was abandoned.

Gramiccia & Beales' (1988) review of "the recent history of malaria control and eradication" presents a detailed analysis of WHO antimalaria expenditures, but omits mention of the vastly greater U.S. congressional expenditure or the massive force of technical personnel required for its conduct. "Dr. P. Russell of the USA, consultant to WHO" is mentioned in passing. Their analysis of the history of the open-ended global program of 1955 through 1969 does not consider the closely reasoned and more intensive worldwide program of 1958-1963.

A decade after its inception, the architect of the IDAE Report reviewed the outcome of the program that he helped create (Russell 1968). After listing its successes and failures, Russell concluded his retrospective with the words "the credits now greatly overshadow the debits. Nothing in the history of public health, it seems to me, equals in determination, accomplishment, and generosity, the performance of the United States in its fight against malaria at home and abroad." After another decade, a memoir written by one of the leaders of this AID effort emphasized the role of WHO and enumerated "Some 37 countries [that] have been certified by WHO as having achieved eradication of malaria. However, this leaves nearly 50 other countries which attempted eradication and did not succeed." (Smith 1977). AID and WHO eradication efforts produced mixed results.

Antimalaria strategies became transformed by the 1980s. The AID program specified that a "country requesting assistance in controlling its malaria problem [must] make a commitment of long-term support of the proposed program." (Anonymous 1983). The tactical nature of the intervention should be designed in a spirit of "maximum flexibility." Research and training are "the keys to long-term success." Most strikingly, eradication was redefined as ending "when certain [prevalence] requirements are met" rather than some predetermined time. The recommendations pointed toward the idea of sustainability as well as affordability and attempted to comply with the Declaration of Alma Ata (Health for All by the Year 2000) by introducing primary health care and the idea of community participation into the antimalaria armamentarium. Thus, programs were horizontalized from the eradicationist vertical mode of administration. Research, particularly aiming toward vaccine development, became a high priority. AID established research efforts under the Office of the Science Advisor and in the Bureau of Science and Technology in Health and a TDR Programme was established at the main offices of WHO. A series of future-oriented programs of research thereby came to replace the more immediately beneficial goal of time-limited interventions.

Despite these conceptual changes, many local antimalaria programs remain locked in the mode of the late 1950s. Prevalence estimates for the previous and for the current year are displayed prominently for visitors' inspection. Progress is measured over a 2-yr span, and failure of reduction of the annual parasite index is attributed to inadequate indoor residual spray coverage.
However misleading, simplicity renders this doctrine attractive.

The unified antimalaria tactic of indoor residual spraying no longer is applicable. Because insecticide resistance now tends to hinder intervention efforts, and because drug resistance impedes prophylaxis and therapy, our ability to intervene against outbreaks has diminished. Despite periodic episodes of fascination with an array of intervention technologies (alternative insecticides, medicated salt, drug administration, genetic control, biological control, antimalaria vaccines, impregnated bednets, and transgenic vector mosquitoes), no antimalaria panacea should be expected. Instead, a series of strategies and administrative structures that are most conservative. They should serve a limited region rather than a geopolitical entity, help promote the general economy of the local population such that program responsibility can devolve ultimately on indigenous agencies. Ideally, such interventions would be applied occasionally in time and irregularly in place; global solutions tend to be most dangerous. Although powerful and useful means of intervention are already at hand, vigorous research efforts are required to increase this armamentarium. The opportunity lies in interpreting our rich store of antimalaria experience and in devising novel strategies and administrative structures that are appropriate to particular local situations. These considerations persuade us to seek small gains.

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ARTICLES

Plague (Yersinia pestis) in Cats: Description of Experimentally Induced Disease

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ABSTRACT Sixteen healthy cats were fed a 6-wk-old laboratory mouse that had died of experimentally induced Yersinia pestis infection (strain NM77–538), to simulate oral exposure to plague. The cats were closely monitored after ingestion. Physical exams were performed and vital signs were recorded daily. Plague antibody titers and cultures of blood, throat, and oral cavity were performed daily. Complete blood counts and biochemistry panels were performed every 3 d. Complete necropsies were performed on any cats that died. Cats exhibited one of three responses following ingestion of one plague-infected mouse; they either died (6/16 or 38%), developed transient illness and recovered (7/16 or 44%) or showed no signs of illness (3/16 or 19%). A continual fever greater >40°C was associated with a poor prognosis. The highest antibody titers developed in the group that shed the plague bacillus over an extended period of time. Blood, throat, and oral cavity cultures positive in 100% of the fatal Throat cultures positive 75% of the exposed In contrast other carnivores, infected with Y. pestis exhibit bubo formation and pneumonic lesions similar to those seen in people with plague. Because of the potential transmission of Y. pestis from cats to people, development of plague vaccine for cats may be warranted.

KEY WORDS plague, Yersinia pestis, cat

WILD RODENTS, most notably squirrels, and their fleas are the primary sources of human plague infection in the western United States. In recent years it has become apparent that domestic cats provide an important link between plague infection in its usual hosts and humans (Thornton et al. 1975, Poland & Barnes 1978, California Department of Health Services 1980, Kaufmann et al. 1981, Barnes 1987, Werner et al. 1984, Weniger et al. 1991). At least 15 human plague cases are known to have originated by direct contact with infectious body fluids or excretions from plague-infected cats (CDC 1979, CDC, unpublished data). Another five cases are strongly suspected to have originated in the same manner. Seven of the 15 proven cases (46%) and 2 of the suspect cat-acquired cases (40%) were fatal. Four of the 15 cases (27%) acquired primary plague pneumonia by inhalation of Y. pestis-infected droplets expelled by cats with secondary plague pneumonia. Four of the 15 cases (27%) occurred in veterinarians or their assistants (CDC, unpublished data).

Domestic cats have long been known to be susceptible to plague and to suffer mortality from the disease (Simpson 1905). The feline response is in contrast to raptors and other birds; wild carnivores, including black bears, coyotes, badgers, skunks, and raccoons; and domestic dogs, which are remarkably resistant to Y. pestis infection. Current information concerning responses of cats to infection is based on observations of pet cats in clinical situations from epidemiological investigations (Kilonzo 1980, Eidson et al. 1988, Eidson et al. 1991). Except for one limited study involving only four cats (Rust et al. 1971), no experimental studie s are represented in the literature.

The objectives of this study were to characterize the pathogenesis of plague in domestic cats, clarify their actual and potential role(s) in the epidemiology and epizootiology of plague—including the risk of infection transmitted from them to cat owners and veterinarians—and to evaluate the humoral immune response of cats exposed to Y. pestis.

Materials and Methods

Facilities. Experiments were conducted at the Painter Center for Laboratory Animal Research,