

**The Edna McConnell Clark Foundation's
Tropical Disease Research Program:
A 25-Year Retrospective Review
*1974-1999***

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The Assessment Process

After discussing the Foundation's goals for the Tropical Disease Program (TDR) assessment with the President and Director of Assessment, the project team reviewed Foundation:

- Records, including Board of Trustees and Advisory Committee meeting minutes;
- Program plans and updates;
- TDR Program and aggregate Foundation program evaluations;
- Descriptions of major grants;
- Key memos; and
- A sample of site visit reports.

The team compiled aggregate Foundation grant funding information, and reviewed written materials from the World Health Organization and pertinent tropical medicine literature. Members of the team attended a Foundation-supported TDR grantee workshop on onchocerciasis held at Woods Hole, and a meeting on Public/Private Partnerships held at Harvard University, featuring a case study of the International Trachoma Initiative partnership. Face to face and telephone interviews were held with 37 key informants, representing a broad cross-section of TDR stakeholders. These included several current and prior Board members and Presidents involved with the TDR Program, TDR Program directors and staff, key grantees, numerous scientists and other highly respected key informants from the tropical medicine and international health fields, and representatives of public and private funding organizations and non-governmental organizations (NGOs) involved in tropical disease treatment and control efforts.

A three-member advisory committee, with expertise in the three TDR disease categories, international health, and philanthropy, advised on plans for the draft report through a conference call with the assessment team and the Foundation's Director of Assessment. This group then reviewed the draft report and provided insight and suggestions during a meeting held at the Foundation. Feedback from this meeting, and from Dr. Cook, who also reviewed the draft, was incorporated into this final report.

EXECUTIVE SUMMARY

For a quarter century, from 1973 through 1998, the Edna McConnell Clark Foundation devoted more than \$90 million to the control of debilitating tropical diseases that afflict millions of people worldwide. The Foundation stayed the course with the Tropical Disease Research (TDR) Program for 25 years, a remarkably rare event in philanthropy. Assessing what has been accomplished by the Program, relative to what the Foundation set out to do, provides an opportunity to gauge the results of that investment and to reflect on lessons learned along the way. Although these lessons derive from the Foundation's extensive international experience, they may help to inform the Foundation's new domestic plans to strengthen the nation's capacity to assist young people in impoverished communities to attain their full potential. They also may prove useful to any foundation involved in or considering support of health programs in developing countries.

This assessment endeavors to place the decisions and approaches taken by the TDR Program within the context of the emerging science and international health controversies of the time. These included polarized views about whether to focus on the development and application of control measures versus investment in basic research and vaccine development, on a single disease versus broad primary care integration, and on strengthening in-country research capacity versus relying on developed countries' perceived scientific dominance.

Overall, the assessment reveals that the Foundation created a major philanthropic presence that fostered significant research progress in each of the three tropical diseases it focused on, schistosomiasis (“schisto”), onchocerciasis (“oncho”) and trachoma. Among the cadre of individuals and institutions comprising the TDR field, the Clark Foundation was able to catalyze interest and momentum not only for these three areas but also for tropical disease research as a whole.

Through the three disease-specific programs, as well as through the broader Health of School Age Children (HSAC) Program undertaken late in the TDR experience, Foundation investments yielded important gains in basic immunology research and attracted a cohort of gifted new scientists and international health professionals into tropical disease research. Despite these impressive gains, the goal of developing an effective vaccine for each of the three diseases proved elusive. The Foundation and its partner Pfizer, however, now face the real possibility of achieving significant control of blinding trachoma by treatment with Pfizer's Zithromax[®], surgery, behavioral, and environmental measures. This concerted approach is being undertaken through the International Trachoma Initiative (ITI), an intermediary organization established through a joint partnership between the Foundation and Pfizer. This first intermediary organization established by the Foundation is a promising model for Clark's newly evolving strategy to strengthen institutions that are key to accelerating progress within specific fields.

As a catalyst, the Foundation is also recognized as the major organizing force behind the creation of the Essential National Health Research (ENHR) effort, undertaken by multiple funders to lay out a blueprint for systematically addressing international health research needs. As a grantmaking innovator, the Foundation also can be credited with pursuing a fundamentally entrepreneurial approach to grantmaking that is now becoming widely emulated within the philanthropic field. In all of its TDR programs, the Foundation used this entrepreneurial orientation to identify and solve problems in highly creative ways.

Development of an Initial Program Focus: Schistosomiasis

In selecting a focus for the Developing World Program (later renamed the TDR), the Foundation defined its niche by way of a precise standard: *Given the myriad problems and enormous population at risk, which problem presented the best opportunity to make a meaningful, rather than marginal, impact?* As one of the TDR Program directors recently commented in regard to encouraging foundations to consider entering

international health, *"There are enormous opportunities in international health. Rather than shy away because you think the problems are just too numerous, you can select anything that presents a reasonable opportunity for making an impact, and develop a strong rationale for whatever you select. The challenge is one of determining how to intervene effectively, once you make that choice."*

Thirteen potential program areas were identified and explored during 1973 and 1974; the Foundation selected tropical disease research as the opportunity most consistent with its early interests, and eventually with its "mission" which evolved over time *"to improve conditions and opportunities for people who live in poor and disadvantaged communities."* Among the opportunities within the field of TDR, the Foundation selected schistosomiasis, based in part on advice from scientific advisors. Schisto, a chronic, parasitic disease that affects the urinary and intestinal systems, causes serious kidney and liver damage and can be fatal. Scientific advisors to the TDR Program recommended this focus because the disease was widespread, affecting approximately 200 million people worldwide, had garnered few resources from the research and funding communities, and yet had some promising research already underway that could be built upon. The Foundation's \$2 million in funding for a field that had an annual budget of \$3 million afforded the Foundation an impressive debut into a significant role.

Committing \$32.4 million over the next 20 years, the Foundation's goal was to achieve effective control of schisto and its elimination as an important disease. The objectives were to determine whether immunity exists or can be induced in humans and, if so, to develop a vaccine, develop safe and effective drugs, improve measures to interrupt or reduce disease transmission, and assess the disease's economic and public health significance to generate political will to control it. The strategy involved undertaking a broad-based, multidisciplinary attack, bringing leading scientists into the planning as well as research activities, informing the field, and providing research grants and other services to stimulate and facilitate research progress.

The TDR Program's first director, Dr. Donald Hoffman, used his basic science and management consulting expertise to implement a highly strategic planning approach that established benchmarks and timeframes for achieving them. Staff assessed the “state of the science” of schistosomiasis, and then invested in the “components” deemed essential to its growth, sustainability and eventual success. These components included a systematic plan to overcome technological and scientific barriers as they were encountered. Unusual in basic research funding and viewed with apprehension and skepticism by some scientists, this approach was later credited with contributing to the strategic planning efforts of WHO’s Special Programme for Research and Training in Tropical Diseases (WHO/TDR) as well.

This entrepreneurial spirit also characterized the Program’s interactions with the private sector. The Clark TDR Program was unique in its efforts to spur drug development for schisto through contracts with Parke-Davis, and to pursue patent protection for grantee products, preempting even the National Institutes of Health's (NIH) mandate for grantees to patent their work. Patents are necessary to prevent cheaper copies from being developed and sold, and this protection was vital to having industry agree to take scientific innovations discovered by others and produce and market them.

First under Dr. Hoffman, then briefly under Dr. J. Stafford Lehman, and then under Dr. Joseph Cook, the Foundation provided 691 grants to developed country researchers between 1974 and 1994 for schisto immunology, vaccine and drug development, and epidemiology and control. The TDR Program also held workshops for researchers and published the Schisto Update to keep the field informed. Additionally, the TDR Program created a significant leadership role as a convening authority for other foundations and international health organizations, as well as for the community of tropical disease researchers.

Factors Affecting the Program's Approach and Achievements

Describing the Schisto Program's achievements, and putting them into perspective, requires viewing them within the scientific, regulatory and business factors of the time, all of which affected the Program's trajectory. During the 1970s, when the Program was developed, the scientific and public health communities had been through several cycles of elation and dashed hopes from various efforts to eradicate disease; the cycle was then in its optimistic phase. The cycle first began early in the twentieth century when the Rockefeller Foundation established commissions to eradicate hookworm worldwide (1907) and yellow fever in the U.S. (1915); both failed and diminished the popularity of eradication efforts for the next three decades. But, following the successful elimination of malaria from specific regions and development of a stable vaccine for smallpox, the notion that disease eradication was possible regained favor with public health practitioners. When, in the mid- to late-1950s, the WHO adopted the goals of global malaria and smallpox eradication, optimism for eradication efforts was high (CDC 1993).

While the vaccine-based smallpox eradication campaign concluded successfully in 1977, WHO's malaria eradication effort failed due to a host of factors, including mosquito and drug resistance and rising costs. WHO's failure with malaria—at a cost to its funders and constituents of \$1.4 billion over ten years—renewed the climate of skepticism for eradication campaigns.

It was not surprising, therefore, that in the early-mid 1970s the view of most schisto experts was that multi-faceted interventions were needed to control schisto and its transmission: The reigning approaches included drug treatment, snail control and other interventions to decrease water contact and to diminish contamination of potentially infective waterways. Recognizing the immense resources required to control schisto through these approaches, however, some international program architects of the time favored a “silver-bullet” approach. Highly focused on a “single solution,” such approaches were intended to balance the competing needs of effective health care

provision and resource constraints¹.

The field of molecular biology was just emerging in the 1970s and being applied to immunology. The scientific potential afforded by these techniques (hybridoma, monoclonal antibody and recombinant DNA) created a climate of “immunologic exuberance”; although the field was just getting underway, optimism was high that these advances would help lead to vaccine development over time. The optimism for a schisto vaccine, at the earliest stage of the TDR Program, arose within this climate as well as from previous, more-or-less empiric successes in developing effective vaccines for bacterial and viral diseases, such as DPT, polio, and others.

Ultimately, however, vaccine technology became viewed as the “silver-bullet” to control schistosomiasis. The necessary factors seemed within reach, given the known characteristics of the disease, and a reasonable “scientific likelihood” conferred by the new technologies. A vaccine was viewed as preferable, given the complex nature of alternative approaches to control (such as eliminating the intermediate snail hosts for the parasite before it infects humans).

In spite of these scientific possibilities, the pharmaceutical industry's enthusiasm for vaccine development--particularly those intended for the developing world--was on the decline. Several market and regulatory factors that precluded a sufficient return on investment had dulled industry interest in tropical disease product development. Together, these conditions created an opportunity—and some perceived an obligation--for the private non-profit sector, including philanthropy, to step in. While the 1970s had witnessed few collaborations between the public and private sectors, two successful models did exist. One was the investment by the National Foundation for Infantile Paralysis in the Salk polio vaccine, and the other was Planned Parenthood's early support for birth control pill research. The vacuum created by private industry withdrawal from

¹ Although the terminology differs slightly today, the debate between the relative merits of “horizontal” (comprehensive, integrated services) and “vertical” (focused, single-disease) approaches continues. Some critics perceive that vertical programs have a “black hole” effect, drawing scarce resources away from comprehensive services. Both the vertical and horizontal approaches to human health and disease management have their respective trade-offs however.

much of vaccine development for the developing world provided an important niche for Foundation efforts focused on schisto control.

Program Accomplishments

Program products were numerous and varied. Although the Schisto Program did not achieve its ultimate goal—to create a vaccine or drug to control schisto—strategic investments advanced research that figures prominently in the current state of the field. A 1984 assessment study found that Clark-funded researchers, while representing only 3% of all schisto authors cited by MEDLINE, had published 32% of the schisto immunology articles published between 1970 and 1984; current tallies put the total number of TDR articles by schisto grantees at about 270. The Program cultivated other communications strategies, such as the Schisto Update and workshops, which succeeded in uniting field, clinical and bench researchers by keeping them informed of the latest advances.

Two diagnostic techniques were developed as a result of TDR investments. The first, a radioimmunoassay, was never actually applied in the field owing to technical limitations. Epidemiology and control efforts were furthered through the development and application of ultrasound as a valuable field tool for measuring disease with a non-invasive technique. Nonetheless, some experts have questioned whether, in retrospect, the Foundation had missed an opportunity by failing to develop a low-cost field diagnostic tool to improve surveillance for both targeting treatment and assessing outcomes. Over the life of the Program, the focus of epidemiology and control efforts narrowed to testing specific strategies, particularly targeting school age children. This later led to investments in integrated parasitic disease control efforts through the Health of School Age Children Program, established in 1993.

The Program's Exit from the Field

During the Schisto Program's life, two commercially developed drugs, praziquantel and oxfamiquine, became available to treat schisto. Their availability, combined with disappointing results in identifying promising vaccine candidates, led to the Board's decision in 1981 to phase out of drug development activities. The Foundation gradually phased-out between 1981 and 1994, creating a Schisto Vaccine Task Force as a mechanism to continue to coordinate vaccine research into the future.

The Foundation's carefully staged withdrawal from schisto was predicated on several assumptions: (1) that development of the two drugs met the need for a simple and effective chemotherapeutic means of control; (2) that further investment by the Foundation in chemotherapy was no longer warranted except for treating resistant strains of schisto; and (3) that the schisto vaccine research agenda would continue to move forward under WHO's guidance. Response from the field was as diverse as the field itself; some researchers accepted the Foundation's rationale for moving out of schisto and into other areas while others indicated that the loss of such a major player created a vacuum of resources, and most importantly, leadership in the field.

Development of the Onchocerciasis and Trachoma Programs

In seeking to maintain a "niche" position for itself among the modest fellowship of U.S.-based international health funders, the Board requested in 1981 that staff explore new opportunities for the TDR Program using funds reallocated from schisto drug development grantmaking. After examining several disease possibilities, TDR Program staff recommended programs aimed at preventing blindness from two diseases: onchocerciasis and trachoma.

Onchocerciasis Program Development

Oncho is a blinding parasitic disease transmitted by black flies that breed in flowing water; it is usually referred to as River Blindness. It afflicts about 18 million people, most of them in Africa. The Onchocerciasis Program, running from 1985 through 1998, was solely focused on immunology and vaccine development. Utilizing what staff coined a “rifle-shot approach” the Oncho Program built upon the lessons learned from its predecessor, the Schisto Program. Expending \$21.5 million over 13 years, the Oncho Program utilized many of the processes initially developed for the Schisto Program, including workshops and a Task Force. A major new innovation, though, was the development of research resource “banks” for grantees that supplied needed biological materials and reagents, and DNA “libraries”, essential to basic research and vaccine development.

Oncho Program Outcomes

Development of an oncho vaccine was particularly vexing because researchers had to separate antigens that might confer protection from those that might actually precipitate the disease. Oncho researchers collaborated extensively within and across four interrelated research areas, coordinated through the Oncho Vaccine Task Force. In contrast to the schisto vaccine research effort where the Task Force became part of the exit strategy, however, the Oncho Task Force orchestrated a highly interactive collaboration throughout the life of the Program. As in schisto, no vaccine was developed. But, the strategy yielded other products that helped to advance future research, particularly related to developing a greater understanding of host immune response. As with schisto, Clark’s investments successfully raised the profile of oncho research by attracting and maintaining a cadre of top-notch researchers to the field. According to the one formal evaluation undertaken for the TDR Program in 1994, the Oncho Program can be credited with stimulating a five-fold increase in the number of labs conducting oncho research. The Program produced 50 antigens for vaccine testing, constructed four DNA libraries to support further genomic research, and established a

large communications network that encompasses new worldwide-web based and traditional media (Hoffman 1994).

Throughout the 13-year Program, staff identified the risks associated with such a tightly honed strategy, in the form of opportunity costs. The first option foregone was an investment in a biochemical approach to disease control through the development of a drug to kill adult worms (a macrofilaricide). This was a research opportunity that the WHO had chosen to pursue. The second option foregone related to involvement with the Mectizan[®] Donation Program, established by Merck Pharmaceuticals in 1987. Merck committed to donate Mectizan[®] for the treatment of onchocerciasis through this program. This unprecedented commitment by Merck focused attention on the rationale for the Oncho Program's continued pursuit of a vaccine. Of chief concern to the Advisors, staff and Board, was whether the availability of Mectizan[®] as an effective and low cost means of control *“made the rationale for the vaccine program less compelling.”* TDR staff and Advisory Committee members concluded that *“a vaccine to prevent infection still presents the best long-term solution and that the prospects for a vaccine justify our continued investment.”*

Exiting Oncho

By 1994, even though some promising vaccine candidates had been identified, development was viewed as not imminently attainable despite its progress. Nonetheless, the 1994 Oncho Program evaluation had found that the TDR Program's efforts had moved the field sufficiently forward in terms of basic science and competitive edge that continued productivity and sustainability for oncho vaccine research was likely. The Board approved a recommendation by staff to close out the Oncho Program, and the Program's final awards were granted in 1998.

Trachoma Program Development

The Trachoma Program was developed simultaneously with the Onchocerciasis Program. Trachoma is the world's leading cause of preventable blindness. With some 600 million people at risk worldwide, about 150 million have the infection, perhaps six million of whom have become blind. A chronic progressive disease in children, it is acquired from infection by the chlamydia bacteria that is prevalent in areas characterized by poverty, inadequate sanitation, and poor hygiene. Later in life, it causes eye inflammation that can lead to scarring of the eye directly and through in-turned eyelashes; this scarring may eventually cause blindness.

While the Trachoma Program strategy followed naturally from the Foundation's experience with the Schisto and Oncho Programs, it differed from these by encompassing a broader scientific agenda; it included a significant focus on the behavioral and environmental aspects of disease transmission and control. Between 1983 and 1999, the Foundation invested \$28.1 million on trachoma immunology and vaccine development, and epidemiology and disease control research.

Over time, as occurred in the other two disease programs, vaccine and drug development efforts proved disappointing. In contrast, the epidemiology and control investments were more promising, yielding several important findings, including the effectiveness of face washing as a preventive measure. This prompted staff to recommend a change in strategy to the Board: phase out of vaccine and drug efforts, and concentrate on furthering progress through epidemiology and control.

Trachoma Program Achievements

Research efforts yielded a grading system that could be used to assess severity of the disease under field conditions, verified the efficacy of using tarsal rotation surgery to avert blindness due to in-turned eyelashes, and identified behavioral risk factors and effective preventive measures for transmission. Each accomplishment was significant

alone, but even more so when later incorporated into a four-part strategy to prevent blindness from trachoma. Coined “SAFE” (an acronym for Surgery, Antibiotics, Face Washing, and Environment), the strategy was endorsed by the WHO in its efforts to eliminate trachoma globally by the year 2020 (the “GET2020” Initiative).

Carrying Forward: The International Trachoma Initiative

A major breakthrough occurred in improving the effectiveness of this strategy with the successful results achieved in clinical trials with Pfizer's antimicrobial drug, Zithromax®. The Foundation had been the catalyst in creating the clinical trials, supported by Pfizer and the National Institute of Allergy and Infectious Diseases (NIAID). Compelled by the success of the drug in treating blinding trachoma with a single oral dose, Pfizer decided to establish a drug donation program in partnership with the Foundation, through joint creation of an intermediary organization, the International Trachoma Initiative. The ITI, directed by former TDR director Dr. Cook, is dedicated to eliminating blindness from trachoma using Zithromax® as part of the SAFE strategy. It is initiating this effort in highly focused interventions in five countries.

This not-for-profit/for-profit partnership's “intermediary” organization is designed to carry forward the Foundation's commitment to tropical disease control by becoming a self-sustaining organization through the appeal and compelling power of its purpose and potential, raising funds from other public and private sources to implement the SAFE strategy in developing nations. As the first intermediary organization established by the Foundation, ITI is a potential model for the Foundation’s hallmark future strategy of creating and using intermediaries to help create the elements necessary to advance a field and to strengthen the capacity of key organizations within fields.

Two Additional TDR Efforts

In the late 1980s and early 1990s, the TDR Program expanded its focus beyond schisto, oncho and trachoma into complementary international health efforts. The first

was an attempt to provide a broader, more integrated context for international health research initiatives, a need Dr. Cook strongly promoted. Through a \$200,000 grant to the International Development Research Council in Canada, the Independent Commission for Health Research and Development was established. The Commission's mission was to examine formally the opportunities and barriers for research in the developing world to determine priorities and promote action among the key institutional and national players in international health.

The Commission presented its report Health Research: Essential Link to Equity in Development, in 1990. It contained four key recommendations relating to the core issue of sustainable development, *essential national health research*. The recommendations helped to orient the Foundation's subsequent efforts toward the development of in-country health research resources (including technology and workforce). Well beyond its effect on the TDR Program, however, the Commission's work effectively created momentum within the field of international health toward implementing the plans and approaches advanced in the report.

A subsequent Foundation grant of \$200,000 supported further work on ENHR opportunities in Africa through the Task Force for Health Research for Development, which had been established to promote ENHR. The Foundation's \$400,000 investment, combined with those from 11 other funders, created a long legacy. Today, the Commission's work is carried out by the Council on Health Research for Development (COHRED), based at the United Nations Development Programme office in Geneva (COHRED 2000).

The second effort related to the three disease-specific programs was the Health of School Age Children Program (HSAC). Created in 1993 to focus on capacity-building and operational research relevant to the health of school age children, it was guided by several lessons learned in the three disease-specific programs. First, there was an explicit recognition of the need for integrated health services and the limitation of resources in developing countries to provide them. Second, experience demonstrated that informed

decision-making and policy formulation required reliable and timely data. Experience with schisto and trachoma also supported the belief that programs designed and implemented by host-country nationals were typically more successful and sustainable. A final lesson drew upon the ENHR message gleaned from the Commission's report that developing countries must advance their capacity to conduct essential health research to meet their own health care needs.

Between 1993 and 1998, the HSAC Program unfolded in Ghana and Tanzania, expending \$4.3 million. The projects were not a success, and emphasized some of the difficulties in undertaking in-country implementation efforts. Nonetheless, the HSAC Program is credited with putting "worm control" on the agenda of many funders. Perhaps more importantly, however, the Program provided a critical learning opportunity for the Foundation concerning in-country implementation and also drug pricing, both of which would later prove useful in the Foundation's evolving partnership with Pfizer and the ITI's five-country trachoma control initiative.

Lessons Learned

Several useful lessons have emerged from the TDR Program's 25 years of experience. Presentation and discussion of these lessons is undertaken with a healthy respect for the maxim that "*hindsight is always 20/20.*" As Mr. Emery cautioned, "*trying retrospectively to recreate the path from TDR to ITI as a map for the future would be like cold fusion. Serendipity played a role.*"

Although these lessons have arisen from an international program focus, and from the relatively technical field of tropical disease research, they address some fundamental aspects of grantmaking that may provide helpful insight for the Foundation's new approach to helping to strengthen the field of youth development. For the most part, they can be distilled into six key elements. A few examples are used within each to illustrate the points.

- 1. Strategic planning provided an essential framework. It worked best, however, when assumptions were made explicit, and when the planning process was flexible enough to take advantage of opportunities and to adjust to a constantly changing environment.**

The strategic plans for each of the TDR programs served several essential purposes. They provided a focus and direction that oriented the Board, staff, and grantees to the goals, objectives and means for each of the programs. They also provided a mechanism for scientific leaders to contribute to the planning process, and to share "ownership" of the approach. Nonetheless, assumptions--both scientific and operational--were not always made explicit. This made it more difficult to challenge the "conventional wisdom" and the assumptions underlying it, and to adjust the planning accordingly.

- Scientists assumed that resistance to the drug praziquantel would occur over time [diminishing the role of drug therapy in schisto control efforts]. This provided a rationale for pursuing a schisto vaccine as essential to long-term disease control. Resistance has not yet occurred to a significant degree, however. It is unclear whether this assumption was reexamined during the extended 13 year commitment to vaccine development through 1994.
- While plans relied on the likelihood that industry would undertake further development and production of vaccines once promising candidate antigens were identified, this crucial assumption did not seem to have been investigated explicitly. NIAID is currently encountering difficulties in stimulating industry interest in developing experimental vaccines to test the several antigens identified to date, most of which were initially explored by Clark Foundation grantees.
- The projected timeline for vaccine development was estimated early in the evolution of molecular biological and immunological tools. It is not clear whether a critical assessment of these tools' applicability to vaccine development

was reevaluated over time as the complexity of the underlying basic science became better understood. Experience, such as that revealed by NASA's strategy to land a man on the moon, suggests that a strategically directed research agenda may work best when the essential scientific components are known and mainly need to be coordinated. The TDR Program's directed approach was a much higher risk since it appears to be ahead of the "readiness" of the science.

- Nonetheless, calculated risk-taking can play a crucial role in philanthropy, which has the "luxury" of resources regardless of program outcomes. For instance, risk-taking in the School Age Children's Program did not result in anticipated program outcomes, but it did produce some unanticipated benefits when staff explored prospects for a two-tier pricing system for SmithKline's albendazole, the recommended drug treatment. The knowledge and experience gained through this negotiation process was of tremendous advantage when the opportunity to collaborate with Pfizer arose. A foundation colleague summed it up aptly: *"In the grantmaking business, if all your programs succeed, then you're not taking enough risks."*
- Assumptions were made explicit in the "rifle shot" approach of the oncho vaccine program. Staff and the Board made the explicit decisions to pursue a narrowly focused effort, which was a high risk/high yield approach. Narrow approaches run the risk of becoming a funding "sink-hole," particularly for niche players, yet unanticipated successes or even incremental products can justify the investment in the end.
- Additionally, the Oncho Program's initial plan--which assumed that essential research resources were available--was challenged by workshop participants. This resulted in development of a highly coordinated research resource capacity that has been credited with greatly accelerating progress on differentiating protective from deleterious antigens.

- The strategic updates late in the Trachoma Program reflected a plan to phase out of the sole remaining area of epidemiology and control because research had established the potential utility of the SAFE program, which was being incorporated into the WHO's GET2020 Initiative. Yet, TDR Program staff recognized the exciting potential of Pfizer's Zithromax[®] to improve the antibiotic component of the program, and rapidly and effectively catalyzed clinical trials that demonstrated its superiority over existing products. This ability to recognize and foster opportunity, and the flexibility to adjust plans accordingly to coordinate the trials and to establish a partnership with Pfizer, has been a striking advance for the field.
 - The Health of School Age Children Program was an attempt to merge the notion of geographic focus, a domestic program theme, with the notion of helping to build in-country capacity. The Foundation assumed a shared theme among domestic and international programs would work, however, this approach forced artificial similarities that were not practical or in the best interests of the participating countries. Problems in developing necessary in-country relationships and the support of major stakeholders emphasized the mismatch between the Foundation's objectives and the countries' internal priorities.
- 2. Assessing, or "field testing" innovations to determine if they work in practice provided vital feedback for refinements.**

Undertaking development of disease control tools, such as drugs and diagnostic agents, was most successful when it was followed by operations research to determine optimal means for implementation. This has critical implications for sustaining field-building efforts.

- The rationale for developing a diagnostic tool for schisto was to improve surveillance outcomes and targeting of treatment with praziquantel. But, the test developed was underutilized, largely because the cost of praziquantel failed to

decline to affordable levels, rendering the test irrelevant. This and other information on praziquantel did, however, lead the TDR Program to support efforts to make a cheaper version of the drug.

- Operations research was used to assess the efficacy of surgery undertaken by nurses in correcting trichiasis (inward-turning eyelashes) in trachoma, followed by nurses training. Subsequent studies have established the effectiveness of this surgical intervention in preventing blindness from trachoma.
- 3. Formal, external evaluation was rarely used, and the TDR Program missed an opportunity for information that might have helped guide or alter its course.**

The TDR Program did not involve evaluators prospectively, during program design and implementation, and it appears that staff did not develop an explicit understanding of whether, and if so how, desired outcomes were to be measured. By failing to define operational definitions of expected Program outcomes, it is likely that grantees did not understand fully the criteria that would be used to determine if they should continue to be funded. Instead, the TDR Program used progress toward scientific benchmarks. While this provided critical information on tactics, it did not assess overall direction and relevance within a changing environment.

- When scientific objectives were not met, there may have been a tendency to focus on redefining *means* rather than on reassessing *objectives*. In the one formal evaluation undertaken, of the Oncho Program, outside evaluators' assessment produced a shift in the Program's direction to concentrate on key areas of opportunity that would advance the field and position it to garner competitive funding from other sources as an exit strategy.
- The absence of formal evaluations places even greater reliance on *post hoc* analyses of quantitative data reflecting the status of specific aims. The process of

an evaluation, however, can be valuable in revealing qualitative aspects that may be otherwise overlooked. Even simple outcomes analyses can provide useful ongoing status updates, such as the schisto immunology literature review conducted in 1986. Although this report provided strong evidence of the contribution of Foundation-funded grantees to the field's scientific literature, such studies were rare. Additionally, there was no explicit tracking and no attempt made to count the number of new scientists attracted into tropical disease research, even though this was an explicit objective of the TDR Program.

- Independent verification, through outside evaluations, can be an important adjunct to information available to the Board to carry out its stewardship role, particularly in highly technical fields. Board members have relied upon the excellence of and trust in the TDR Program directors, and on input from program advisors who are recognized to have to balance their self-interest against "objectivity." This process is generally acknowledged to be imperfect but largely effective. Program evaluations will not perfect the situation, but would be additive.
 - Planning and evaluation of the ITI's activities is based, in part, upon epidemiological data provided by each of the pilot sites. Strategic plans should include quality control measures to assure the availability and reliability of necessary data. Because the ITI is in an early stage of development, serious consideration should be given to developing and undertaking a prospective evaluation.
- 4. With experience, the exit strategies became progressively better developed and implemented.**

Staff recognized over time that exit strategies were needed to help strengthen the capacity of researchers to build upon Foundation-funded gains and to progress in the absence of continued funding. The ITI may represent the first exit strategy to identify fully the factors that are both necessary and sufficient for continuing to progress toward

the goal(s), and by determining feasible means to assist these efforts to become self-sufficient. As such, the ITI may provide an important model for the Foundation's newly evolving institution-and-field building approach.

- While schisto researchers were grateful for the gradual withdrawal from the field, the only mechanism developed to facilitate continued progress on a schisto vaccine was establishment of the Schisto Vaccine Task Force and short-term support to WHO to sponsor it. This was insufficient to promote continued progress. NIAID and the European Union have continued to support schisto vaccine research, but have not been successful in finding industry sponsors to undertake development of promising antigens. Thus, neither the public nor private sectors has created conditions necessary to sustain the work.
- Lessons learned from the Schisto Program informed development of a strong exit strategy for the Oncho Vaccine Development Program. That Program's exit was facilitated by its grounding in a progressively more tightly focused strategic plan, and the early creation of mechanisms to produce and provide research resources and to foster collaboration. Nonetheless, the Foundation recognized that even while these advantages would put the researchers in a stronger position to compete for NIH funding, continued progress on an oncho vaccine was not assured. While in the short-term funding for oncho vaccine development will decline, the potential for sustained progress is greater than it was for schisto. Evidence of this includes newly created funding sources and organizational linkages, current NIAID funding of key investigators, recent scientific “breakthroughs,” and the exchange facilitated by the OnchoNet website. It is clear, however, that the ultimate goal of a safe and effective vaccine for human use lies far in the future, and will be difficult to achieve (as with schisto), without active participation of industry.
- Initially, the exit strategy for trachoma was similar. For the vaccine work, the strategy was to leave future research efforts to the NIAID where they might be

incorporated into ongoing chlamydia research on genital tract and lung infections. But with the promising early studies of Zithromax[®] in treating trachoma, the exit strategy took a major turn and focused on helping to establish the drug's efficacy as part of the SAFE strategy. It then progressed to development of a partnership with Pfizer to design and implement a drug donation program as part of this strategy. This institution and field-building effort will become dependent on other funding partners, on effectively managing complex relationships with a host of international and in-country agencies and NGOs, and on continued commitment of Pfizer to donate the drug for the long-term. An assessment of these and other factors necessary for sustaining progress toward trachoma control would be a valuable contribution to the field of field building.

- For instance, the ITI has, in essence, “captured the field” by virtue of its exclusive arrangement with Pfizer to utilize Zithromax[®] in the elimination of blinding trachoma. However, Pfizer will lose its worldwide patent for Zithromax[®] in 2001 and its U.S. patent in 2005. What are the long-term implications of these eventualities for Pfizer's continued donation and for funding from other sources? If necessary, will ITI have the funding to responsibly exit the field?

5. Strong, clearly-defined working relationships were an essential hallmark of successful TDR Program activities.

The TDR Program demonstrated that successful collaboration required knowing the strengths, limitations, public perception, and culture of collaborating organizations, and designing collaborations accordingly. This has critical implications for institution- and field-building strategies. Providing pilot or small-scale grants to potential collaborators was an often used and effective means for assessing their strengths and limitations.

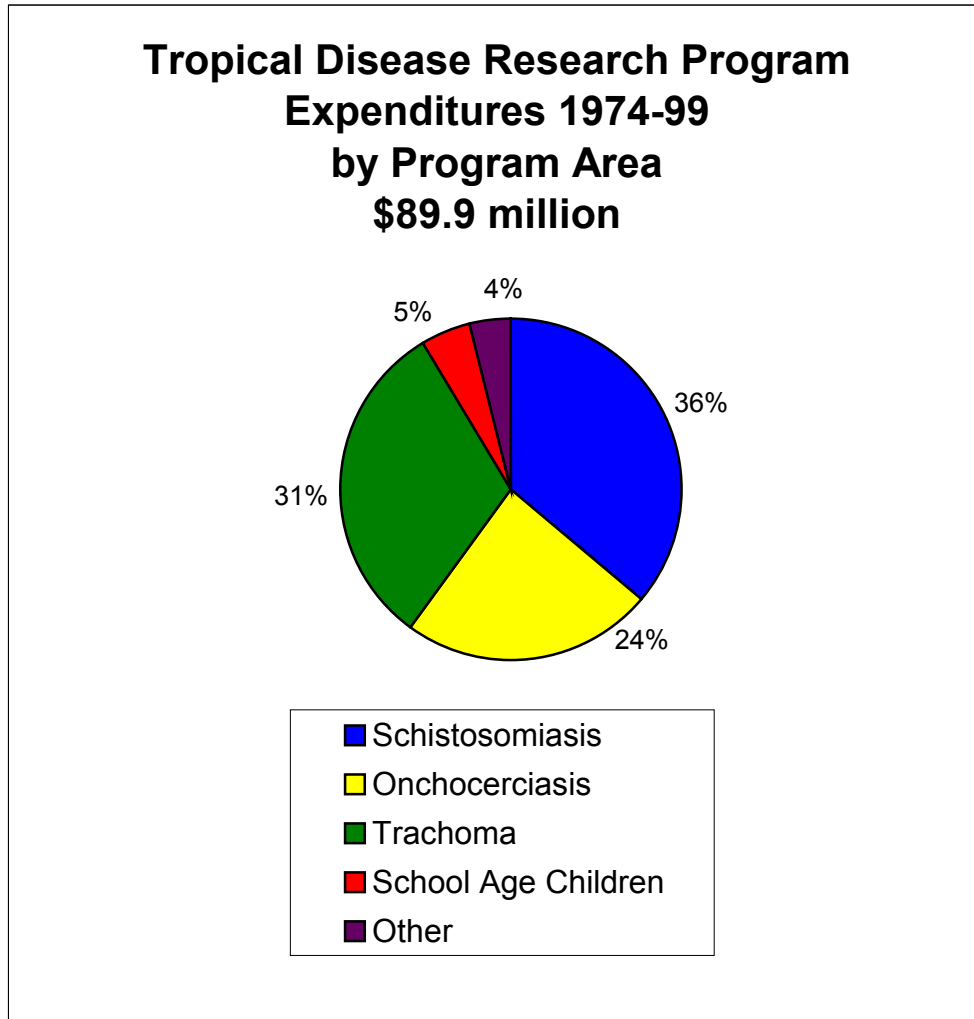
- Strategic alliances with the WHO were based on first-hand experience with WHO's Tropical Disease Research and Blindness Prevention Programmes, the

context within which they operated, and on an understanding of which goals the two organizations shared, or conversely, what unshared goals might be complementary. For instance, knowing the financial and political factors that limited WHO/TDR's long-term commitment to oncho vaccine development created an opportunity for the Foundation that its colleagues at WHO welcomed.

- Pilot grants provided to collaborating organizations helped identify strengths that were later called upon in larger scale efforts. This included the NGO Helen Keller International's expertise, flexibility, and strong networking in the field that were revealed by earlier grants and later called upon to provide the initial home of the ITI. When establishing multi-party alliances, the TDR Program evidenced knowledge of the partners' strengths, organizational capacity, and mission and balanced these against weaknesses and potential conflicts.
 - Important to the successful partnership with Pfizer in creating the ITI partnership was a well-honed understanding of the shared goals of the two organizations, and of an appreciation of one another's objectives and the rationale for these, according to the recent Harvard Business School case study (Barrett, Austin, McCarthy 2000). As one Board member indicated, this partnership is predicated on the common goal of preventing blindness from trachoma, and the economic issues that usually contribute to the breakup of joint ventures is not likely to be present.
 - In contrast, in the Health of School Age Children's Program, the Foundation's lack of understanding of the partners' capabilities, objectives and means of operations hindered collaboration and limited the Program's success.
- 6. The TDR Program's entrepreneurial approach to grantmaking sought to create sustainable conditions, in the absence of a viable private sector market, and this may stimulate ideas for working with industry to help build capacity in other fields.**

- In one approach, the Foundation sought to "take matters into its own hands" by supporting research on the development of a cheaper alternative to praziquantel for treatment of schistosomiasis.
- In another approach, the Foundation developed its own industrial process, by providing support to industry (Parke-Davis) to work on drug development directed by the Foundation, and grants to academic institutions to carry out carcinogenicity and animal testing functions that are an essential part of drug development.
- The Foundation took out patents on grantee product therapeutic and diagnostic innovations, to help facilitate industry willingness to further develop, produce and market products by barring competition from cheaper copies.
- In the case of ITI, the Foundation first catalyzed the studies necessary to demonstrate efficacy, and then developed a working partnership with Pfizer to develop, coordinate and assess drug donation incorporated into the SAFE strategy. This latter approach may prove to be a hallmark in private sector for-profit, not-for-profit ventures.

Figure 1: Tropical Disease Research Program Expenditures 1974-1999, by Program Area



ACRONYMS

CDC	Centers for Disease Control
CGIAR	Consultative Group on International Agricultural Research
COHRED	Council on Health Research for Development
ENHR	Essential National Health Research
FDA	Food and Drug Administration
HKI	Helen Keller International
HSAC	Health of School Age Children
IH	International Health
ITI	International Trachoma Initiative
MDP	Mectizan [®] Donation Program
NASA	National Aeronautics and Space Administration
NGO	Non-Governmental Organization
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OTF	Oncho Task Force
PCD	Partnership for Child Development
ROI	Return on Investment
SVTF	Schisto Vaccine Task Force
TDR	Tropical Disease Research
UNDP	United Nations Development Programme
WHO	World Health Organization
WHO/TDR	World Health Organization Special Programme for Research and Training in Tropical Diseases

I. Introduction

It was during a return flight from earthquake-damaged Managua, Nicaragua in 1973 that the idea of a potential Foundation role in tropical disease research first took root. The notion arose as Donald Hoffman, Ph.D., the Foundation's new recruit in charge of exploring international, and science and technology options, discussed possibilities with Foundation President James ("Jim") Henry.

The Foundation's interest was broad, "for the benefit of mankind," which over time became defined more specifically to improve conditions and opportunities for people who live in poor and disadvantaged communities. *"We had decided to view the option of the whole world,"* Dr. Hoffman (now a practicing MD pulmonary/critical care specialist) recalled recently. With a doctorate in biophysics, a minor in history, and experience working in Tanzania for McKinsey Consulting on the government manufacturing sector's import/export issues, Dr. Hoffman had spent his first year at the Foundation gathering data on potential international and science and technology opportunities.

According to Dr. Hoffman, Mr. Henry's notion of how the Foundation should function was key in orienting the exploration. *"Jim thought the Foundation should leverage other resources, be a venture capitalist of ideas, hire broad generalist consultant types, and use planning and audit to initiate and refine efforts over time. John Emery helped to define the guiding principles...Just as the Gates Foundation is now using venture capital and setting out expected results in its international vaccine efforts, Jim Henry operated under that philosophy thirty years ago."*

"Originally, the Foundation did not seem interested in international grants--it was too big. But Avon was an international sales company...We had three outside experts to critique and help us select among choices. George Harar was one of the advisors; he was an architect of the institutional structure that led to the Rockefeller Foundation's Green Revolution. Robert McNamara, President of the World Bank at the

time, was another of the advisors, and wanted a role for the Foundation in world population, but we couldn't find a leverage point...I presented several areas to them, including an international disaster relief system, and an effort to improve the effectiveness of management training in lesser developed countries, essentially to create middle management...On the flight from Managua, Jim [Henry] and I decided international health was too big an area. But, tropical disease might not be."

It was the early 1970s, and the prevalence of major tropical diseases had reached more than one billion in the developing world. In several instances, increases in prevalence were an unintended consequence of development, for example large-scale rural development projects having water resource components. These new sources of water for irrigation and hydroelectric power served also to enhance the transmission of diseases such as schistosomiasis ("schisto") and malaria.

While the Foundation also considered the other areas Dr. Hoffman had suggested, including developing an emergency relief system, management training capacity in lesser developed countries, and crafts as an economic growth vehicle for developing nations, tropical disease research quickly emerged as the recommended direction. According to John Emery, a Trustee since the Foundation's founding, *"Since we had made the decision to be involved in the international area, had a relatively small amount of funding to devote to it, and had Dr. Hoffman on staff, health was a natural area that had potentially high leverage possibilities. The need was horrendous. And the possibility of helping a lot of people who were suffering from diseases, by investing a relatively small amount of funding, was very attractive."* Although some National Institutes of Health (NIH) scientists discouraged Dr. Hoffman from pursuing a role in tropical disease research, he saw potential. *"Leverage point analysis revealed that tropical disease was way underfunded per capita. Of the U.S. groups, only the military was providing sizeable funds for pursuit of prevention and treatment product research, and developing countries did not have an inside track to address issues of concern to them. So, we came up with names of people to advise us on tropical disease and on using a workshop mechanism, including Ken Warren (Case Western Reserve), Tom Weller (Harvard School of Public Health and a Nobel Laureate), Gordon Smith and George Nelson (London School of Tropical*

Medicine) and Herbert Giles (Liverpool School of Tropical Medicine)... *I developed a strategic plan to present to scientists in the field, and got many of them out of joint by it...My plan was to co-opt scientists into buying into planning, and to get their input so they would help shape and have ownership in a specific plan.*”

Dr. Hoffman convened a workshop in St. Lucia in 1974, and charged the participants with determining which tropical disease to target, and subsequently with helping to develop and maintain the strategic plan and research process, and with providing oversight and technical guidance along the way. The Department of Defense was already spending \$4 million annually on malaria. *“So, we chose schistosomiasis for several reasons. It was not so distant a goal as to be hopeless. Research was already underway (supported predominately by the Wellcome Trust and Medical Research Council of Great Britain, and to a lesser extent the NIH) so there was already a good cadre of researchers who were the nucleus. Participants advocated emphasizing epidemiology and parasitology. I wanted to add molecular biology and immunology, sciences of the future.”*

With contributions from a range of scientists, the initial plan was expanded during and following the St. Lucia meeting. Some contributors, such as Dan Colley, Ph.D., a promising immunologist at Vanderbilt University, urged that the plan be sufficiently broad to enable Foundation staff and advisors flexibility in selecting areas to emphasize over time. He and others believed that care should be taken not to exclude promising scientists and disciplines.

“ I set out to apply modern business techniques to optimize our limited resources to achieve the highest leveraging possible,” Dr. Hoffman recently commented, “and initiated this with a strategic plan. This was a departure from the funding mode of the time used for supporting research, particularly for basic research.” As the TDR Program emerged and evolved over the subsequent 25 years, the Foundation contributed nearly \$90 million. The Program was led first by Dr. Hoffman, then briefly under Dr. J. Stauffer Lehman of Harvard, and for 20 years under Dr. Joseph (“Joe”) Cook. Initially,

and for the next seven years, it focused solely on schistosomiasis. The TDR Program was entrepreneurial in nature, seeking ways to stimulate investment by others, taking a venture capital approach, and establishing a timetable for achieving specific scientific benchmarks in the development of a vaccine to protect against schistosomiasis, drugs to treat the disease, and epidemiological knowledge to provide a basis for the development of rational control measures.

Program operations would fill the deficits in fundamental knowledge, appropriate control tools, and planning efforts to solve the problem. The TDR Program's roles were to guide results-oriented research, attract “new research talent,” and to catalyze planning and funding of schistosomiasis control by governments and international agencies.

In industry-like fashion, work was focused on specific scientific targets. As issues arose, entrepreneurial paths guided removal or circumvention of barriers. For instance, when research led to potential development of products, the Foundation took out patents in collaboration with grantee universities. Patents provided a 17-year period of protection (extended recently to 20), blocking the marketing of any identical products that could be sold more cheaply. Seeking patents for products and/or their processes and uses was highly unusual at the time for non-profit organizations, and preceded the NIH's policies in the early 1980s of encouraging researchers to patent their grant-supported intellectual property.

Equally unusual was the Foundation's support to industry, another entrepreneurial tactic. Parke-Davis received funds to undertake chemical synthesis of potential anti-schistosomal agents. University researchers received funds to test the chemically synthesized agents in mice, and to evaluate simple biologic systems for detecting potential carcinogenic effects of antischistosomal agents. Essentially, this established the same type of development and testing process used by industrial firms. Additionally, the Foundation supported a survey of U.S. pharmaceutical companies engaged in tropical disease research to determine the origin, regulatory histories and fates of all new drug candidates tested in humans for tropical diseases. This would help identify potential

barriers that the Foundation would need to address in its efforts. Another entrepreneurial avenue was taken when an effective drug for treating schistosomiasis became available but was too expensive for developing nations to purchase. The Foundation funded efforts to develop a cheaper alternative.

Despite this highly entrepreneurial approach, the ultimate goal of developing a schistosomiasis vaccine remained elusive and eventually the Foundation chose to exit the field. While Foundation-supported researchers contributed significantly to the field, a cadre of new scientists were attracted into schistosomiasis research, and some important products and processes were developed, the Foundation staff was concerned that they had not created a mechanism for continuing progress in the absence of grant funds.

Entrepreneurialism also guided the Program's subsequent development of initiatives in the mid-1980s to improve control of trachoma and onchocerciasis (“oncho”), two leading causes of preventable blindness in the developing world. During efforts to develop a vaccine for oncho and a vaccine, drugs and epidemiological control for trachoma, the TDR Program added another unusual practice, developing “resource banks” for investigators. For instance, as DNA technology progressed, the Foundation developed a genetic tissue “library” for researchers to use in laboratory studies. Oncho researchers were able to obtain critical infective material from Foundation-supported tissue banks when such materials were otherwise unavailable. Nonetheless, as in schisto, development of an oncho vaccine also proved elusive, and the Foundation exited the field, leaving to others a number of research contributions and a well-functioning consortium of scientific collaborators.

Through the Trachoma Program, the Foundation recently entered into a promising entrepreneurial partnership with Pfizer. The partnership is designed to enhance implementation of the current strategy to eliminate blinding trachoma using Pfizer's antibiotic, Zithromax[®]. When Pfizer decided to donate Zithromax[®], the two organizations created a promising not-for-profit/for-profit “intermediary” organization, the International Trachoma Initiative (ITI). The intermediary is designed to marshal and

coordinate efforts by others, carrying forward the Foundation's trachoma commitment through grant support intended to raise funds from other public and private sources to implement the SAFE strategy in developing nations. The SAFE strategy was developed (largely as a result of Foundation research investments) *"to address the medical, behavioral, and environmental changes needed to control the disease: Surgery to correct trichiasis, Antibiotics to treat active disease, Face-washing to reduce transmission, and Environmental changes to improve water supply and sanitation"* (StrategyMaker Associates, 1998).

ITI is the first intermediary organization established by the Foundation, and is a potential model for the Foundation's hallmark future strategy of creating and using intermediaries to help create the elements necessary to advance a field and to strengthen the capacity of key organizations within fields. The ITI, under Dr. Cook's leadership and with support from the Foundation and Pfizer, is implementing the SAFE strategy in five countries. Pfizer is donating Zithromax[®], and the ITI is coordinating all elements of the strategy.

What created the need for this trachoma initiative intermediary? Largely, it is the struggle by this (and other) foundation(s) to determine how to sustain their efforts after they decide to exit from a field. It cuts to the crux of the issue for foundations: *How can they help to create conditions that will sustain progress toward their goals (without limitless funding) in the absence of a market response?*

The lack of a market for products to prevent or control tropical diseases is reflected in pharmaceutical industry-related data. Africa, where tropical diseases flourish, accounts for 1% of pharmaceutical world drug sales, while the United States, Western Europe and Japan account for 80%. Between 1975 and 1997 only 13 (1%) of 1,233 new patented medicines were for tropical diseases (McNeil 2000).

What created (s) the lack of a commercial market for vaccines and drugs for diseases endemic in developing countries? Largely, it has been attributed to four market-

related factors that have stood to preclude a sufficient return on investment (ROI) on these, and on many other, types of products. One factor is higher research and development (R&D) costs that resulted from legislation enacted in the 1960s that requires manufacturers to demonstrate both safety and efficacy of drugs and vaccines. A second market-limiting factor is lack of patent protection, which leaves developers open to competition from identical ("generic") copies that can be produced more cheaply. Types of unpatentable products include natural substances, shelf chemicals, and drugs already "known to exist" (often through descriptions in the literature). A third market limiting factor is liability risks, and a fourth is distribution problems, especially for products intended for use in developing countries.

Market Limiting Factors: Higher R&D Costs

The most significant among these four factors are the 1962 Amendments to the Food, Drug and Cosmetic Act. Prior to the Amendments, the Food and Drug Administration (FDA) only regulated drug safety, and moreover, it was the FDA's responsibility to demonstrate that a manufactured drug or vaccine was not safe. The Amendments required manufacturers to demonstrate that drugs were both safe and effective before they could be sold in interstate commerce.

The Amendments strengthened greatly consumers' access to quality (safe and effective) products, but at a substantially increased cost to manufacturers and ultimately to consumers through drug prices. A casualty was a loss of interest in developing drugs that were not expected to provide a decent ROI. While pharmaceutical manufacturers had become dependent back in the 1950s on producing a few market winners to generate most profits, other products had to at least break even for firms to remain competitive.

Commenting on the situation in the mid-1970s, Dr. Barry Bloom, a vice-president for research at Pfizer, said that industry had not been making research progress at a rate commensurate with current knowledge and resources on major crippling and lethal diseases, such as products for treating inflammatory diseases (which include some

tropical parasitic diseases) (Bloom 1976). R&D costs that had averaged about \$17 million per product in 1973, when the TDR Program was just beginning, were estimated at \$54 million by 1976. This included costs of drug candidate failures, opportunity costs of not investing funds spent on R&D, and direct drug research and clinical testing costs (Hanson 1980). During the TDR Program's 25-year history, industry cost estimates had reached \$235 million on average per new product (DiMasi 1991).

Another Market Limiting Factor: Patent Protection

Patent protection was the make or break issue when the National Cancer Institute (NCI) set up a screening program in 1955 to try to interest industry in seeing whether any of their chemicals might be effective against various forms of cancer, each one of which represented a relatively small market. In a dramatic demonstration of the critical role patent protection played, only one company (Upjohn) participated until the NCI agreed not to seek assignment of patent rights, and leave these solely to industry. Within a few years of striking this deal, the program had grown to a \$35 million industrial contract operation (Zubrod 1968), and by 1982, the NCI had played a development role in virtually every anti-cancer drug that had been marketed.

Even patented drugs intended for use primarily in some developing countries faced a special obstacle, however. Several countries did not abide by international patent protection laws, or recognized only patent protection for the process used to make the drug but not for the drug itself. In these instances, once the chemical composition of a drug was determined, the drug could be copied locally, produced, and sold at a low price. A largely successful effort to resolve this problem resulted in the 1994 Treaty on Trade-Related Aspects of Intellectual Property Rights (McNeil June 2000).

Vaccine Disincentives: Production, Liability and Distribution Barriers

Uncertain costs, liability risks, and distribution barriers have been especially problematic for vaccines, leaving government (and a few foundations) to play a

significant role in their development. Barriers to industry vaccine development, as summed up in a 1984 National Academy of Sciences assessment, include difficulties and expenses in mounting large-scale human clinical trials, high production costs resulting from the need for separate production facilities, difficult and expensive quality control methods and monitoring, and highly challenging production problems (Widdus 1984).

Liability risks for vaccines are substantial, even for those primarily intended for developing (and less litigious) nations. Insurance actuaries have difficulty rating the risk of administering vaccine to large populations, and judicial rulings have established that vaccine manufacturers can be held liable for failure to adequately warn of risks or for adverse effects that occur, even in the absence of negligence. Vaccine distribution is also vexing, especially in rural areas of developing countries, where transportation is often uncoordinated, and storage, refrigeration, and availability of trained health workers to administer vaccines are insufficient. Add to these factors the anticipated low vaccine sales revenue from nations with miniscule health budgets, and the coffin becomes sealed.

A 1979 Office of Technology Assessment report concluded that low profits, coupled with extensive federal regulations and widely publicized liability cases, had caused the number of vaccine manufacturers to drop precipitously from 37 to 18 from 1967 to 1979. Only seven of these companies were actively producing vaccines in 1979, when the Foundation's efforts in Schistosomiasis were in full swing, and just before the Foundation began to look into additional areas to address. Those seven companies were Pfizer, Merck, Parke-Davis, Merrell-Dow, Cutter Laboratories, American Home Products (Wyeth) and Lederle (OTA 1979).

As the Director of the Center for Disease Control's (CDC) Antiparasitic Drug Service emphasized in a 1977 *New England Journal of Medicine* article, "*Parasitic diseases are the 'cancers' of developing nations, yet total international research expenditures on tropical infectious disease was only \$30 million U.S. dollars in 1975, whereas one 'developed' country alone spends nine times that much on cancer research*" (Schultz 1977). A World Health Organization (WHO) International Medical Sciences

Roundtable at about that time reported that the possibility of developing suitable parasitic disease vaccines had not been explored, although a degree of natural immunity was a well-established sequel to infection (WHO 1978).

In part deriving from these issues, the federal government's role in vaccine development dates back to the 1900s, when federally-funded scientists developed vaccines for Rocky Mountain spotted fever and typhus, while industry developed vaccines for cholera, plague, and rabies. Over the years, the federal role has increased significantly, with the National Institute of Allergy and Infectious Diseases (NIAID) and the CDC becoming heavily involved in vaccine and immunobiologicals research in the 1970s. This has led to improved vaccines for mumps, measles, hepatitis B, pneumonia, and meningococcal A and B infections.

By 1982, when the Foundation was initiating efforts on trachoma and oncho vaccines, NIAID had participated in 14 marketed vaccines or immunobiologicals and in 26 more still in research, including products for tropical diseases. During that same time, the CDC had developed two immunobiologicals and was distributing 14 parasitic disease drugs needed by people in the U.S., including returning travelers (Asbury 1985).

Legislation on Market Protection and Patenting

Drugs of limited commercial but great medical importance came to the attention of Congress in the late 1970s and early 1980s. Recognizing the many disincentives to industry, but focusing specifically on products for diseases or conditions that are rare in the United States, Congress passed the Orphan Drug Act, signed into law in early 1983. The law creates a seven-year period of market exclusivity for rare disease products, even if they are not patentable, during which time no competitor can market an identical drug for the same “orphan” condition. The law also allows tax deductions for 50% of clinical testing costs (Asbury 1985). While the law has been associated with a six-fold increase in drugs and biologicals marketed for rare diseases in the U.S. (Asbury in press), it did not help alleviate disincentives for vaccines for developing nations.

At about the same time (1980), Congress directed federally-funded researchers to take out patents on their inventions or risk having the federal government assume the intellectual property rights on those inventions. The Bayh-Dole Act also required that federally funded researchers license their patented inventions to industry to develop them into marketed products. The Act was designed to speed products from bench to bedside, recognizing that industry alone was capable of turning inventions into mass produced marketed products for the public. Unless these inventions were patented, however, industry would not touch them and risk being undersold by competitors who could copy and produce them at low cost. In the practice of patenting and licensing, the Clark Foundation had been way ahead of this curve.

Philanthropic Involvement

Within this lackluster market environment for development of drugs and vaccines for “unprofitable” diseases and conditions, a few foundation precedents had occurred for stimulating product development. The National Foundation for Infantile Paralysis (NFIP) urged Dr. Jonas Salk to mount an intensive investigation into a polio vaccine, based in part on promising work by NFIP-funded grantees (Schwartzman 1976). Planned Parenthood helped to support small-scale testing of progesterone as a birth control pill, which led to large-scale trials of norethynodral (far more potent than oral progesterone) supported by The G.D. Searle Company (Schwartzman 1976). Similarly, in agricultural advances needed by developing countries, the Rockefeller and Ford Foundations had jointly sponsored research in the late 1950s and early 1960s that led to the development of new strains of wheat and rice that doubled and tripled production per acre (Porter and Kramer 1999).

The Role of Philanthropy in the Absence of a Market

The notion that foundations step in when markets fail to create the conditions necessary for industry involvement is an often-voiced view of the role of philanthropy. As stated in a 1999 *Harvard Business Review* article, “*Instead of competing in markets, foundations are in the business of contributing to society by using scarce philanthropic*

resources to their maximum potential. A foundation creates value when it achieves an equivalent social benefit with fewer dollars or creates greater social benefit for comparable cost.” Later the article states, *“Instead of funding research, many foundations seek to promote innovation through seed grants that are designed to establish and support specific new programs. There is little benefit, however, in starting new initiatives if they do not survive and grow. Too often foundations...fail to support the grantee over an appropriately long time span”* (Porter and Kramer 1999).

How long is an appropriate time span? What occurs during that time span that creates conditions to sustain intended progress once a philanthropic organization leaves the field? The conundrum of how to create the conditions to sustain the goals of philanthropic efforts once a foundation moves out of a project, or a field, is the pivotal dilemma foundations face in working on problems that do not have market potential. This issue was raised directly in a 1989 Tropical Disease Research Program advisory committee meeting by Trustee Sidney (Jim) Weinberg. *“The Foundation is doing what the private sector is not doing, because the private sector is not doing it. In the absence of market forces, to guide planning and development of program goals, what is the substitute for the directing forces of the market? What is the Foundation’s role?”*

In reflecting on this dilemma recently, Mr. Weinberg elaborated. *“The quandary is what a Foundation can do in the absence of a market. The Foundation did its mission with distinction. They had good people. The advisory committee had the best people in the field. They did the best that could be done among foundations that try to do those things. They did not try to avoid market correction. Nobody ducked the issues. But, it is not as good as a power saw that will saw off an arm if it messes with the market. They had a long-term, sustainable commitment that takes guts. The question is, what could the Foundation do, given the mission?”*

By implication, the tacit mission was to intercede in the absence of a market to improve conditions for people living in poor communities. *“It is an unassailable*

positive, how to get at defining the mission to optimize the return on investment? But, it's a bottomless pit. What will sustain the effort?

“Foundations could somehow try to work with the market, create a machine that will function on its own, create a sustainable condition from an economic, scientific, and operational viewpoint. But there are an extremely complex number of variables that incrementally complicate the situation. So, in the end, it comes down to a celebration of good intentions that is so powerful, and so good, that it has an overriding influence on the condition that is needed to sustain the effort.”

For Mr. Weinberg, this issue of a foundation's role in filling the void left by the absence of a market is not confined to drug and vaccines for developing countries. It is inherent in the philanthropic mission itself. *“Look at other programs. The Foundation's jail program used litigation, worked with good people. But nothing more happened with those efforts once the Foundation left the field. Litigation doesn't create a sustainable condition. Legislation does.”* When then Foundation President Peter Bell said in a 1989 TDR Advisory Committee meeting that the Foundation should get to a stage and then let others pick up the torch, Mr. Weinberg responded that *“letting others pick up the torch is different than doing it ourselves.”* His point, he recently explained, is that if a foundation does not create sustaining conditions, it is leaving to chance the likelihood that others will intervene. The question of how to achieve sustainable goals, in the absence of a market, remains a major challenge for Clark and other foundations. It is at the heart of the Foundation's new efforts to use grant funding to build institutions and fields, starting with the ITI, the next promising stage of the Foundation's efforts to control trachoma.

The entrepreneurial approach taken by the TDR Program over the years emphasized determining what was needed and not otherwise available to pursue vaccine and drug development, from research processes to patents, and devising means for creating their availability. In the Foundation's current parlance, this could be considered an approach that was helping to build the field for tropical disease products. The Foundation is now moving to a next stage. It is seeking to enter a field strategically,

determining at the outset what is needed to increase the capacity of institutions within a field, and of a field in general, to continue to progress on their own.

In the 1998 Annual Report, Foundation President Michael Bailin began to outline the opportunities and challenges of this explicit strategy.

“Historically, many foundations, including this one, have invested more in the invention of new strategies and in the requisite research and development that accompanies such invention than in the overall productivity and strength of our nonprofit partners. To right this imbalance, I suggested last year that a more deliberate philanthropic investment needed to be made—both of dollars and ideas—in the organizational strengthening of our grantees and the strategic cohesiveness of the fields in which we work...More and more, our grants have come to reflect this added emphasis on institution- and field-building...”

“Applying those means, however, leads us into partly uncharted terrain. The model of the modern institution- and industry-builder...is the venture capitalist, who has become in many circles a favorite pattern for a more entrepreneurial style of philanthropy. Yet... we’re unlikely to find our course as philanthropic institution- and field-builders with the borrowed cartography of other industries. We need a path that is distinctively philanthropic and yet is grounded in the business disciplines that have built and advanced institutions, technologies, and markets throughout the world. That is not an unreasonable standard, but it demands experimentation and it entails some risks.

“Though these new approaches constitute a shift in emphasis, they aren’t entirely new to us. In fact, the most remarkable event of 1998 at this Foundation—the birth of the ITI—from decades of work in our TDR Program—is a direct consequence of that program’s decade-long effort to build a field of activity from disparate but related disciplines of science, medicine, public health, diplomacy, and philanthropy.

“We regard the ITI to be an essential, final, step in our work on this subject. The organizational health of the Initiative will be as important an element of our TDR Program as were the years of medical and social experimentation that brought us to this stage. So, the trachoma story, remarkable in itself, is also significant for the insight it offers...in general: the critical work of research, invention,

and innovation...is not complete until effective delivery mechanisms are in place to turn new ideas into effective products and services that make people's lives measurably better."

The Foundation has articulated a critical notion that institution- and field-building are necessary to sustain the ability to improve lives through grant-supported efforts. The challenge for the Foundation, and the philanthropic field in general, will be to determine if institution- and field-building are also *sufficient* for sustaining these efforts in the absence of a viable market. If not, there is more work ahead in wrestling with the dilemma of how to create a sustainable condition in the absence of a market. Put another way, can philanthropy help to create favorable market conditions? Or, as Mr. Weinberg suggested, can a Foundation develop ideas that are so powerful and so compelling that they have an overriding influence on the condition?

In the chapters that follow, the history, trajectory, successes and lessons learned from the TDR Program are described within the context of this dilemma, in the hopes that it will be useful to the Foundation in its efforts to reach this new stage of strategic grantmaking toward sustainable futures.

II. The Schistosomiasis Program (\$32.4 million, 1974-1994)

a. Historical Overview of Schistosomiasis

Schistosomiasis likely evolved in central Africa as a parasite of primates, spreading through much of that continent in antiquity and to the New World through the institution of slavery in more recent times. While encompassing several different species of parasites, the disease has two principal clinical forms: urinary and intestinal. In urinary schistosomiasis, bloody urine is often the early sign of infection; over time the infection can lead to severe urinary system damage, including kidney damage and eventual death. In the intestinal forms, signs of infection often do not appear until late-stage damage to the liver has occurred. This may lead to profound dysfunction and death.

In the 1800s, the disease became a major public health threat in Egypt when the Nile River was dammed and massive agricultural irrigation schemes were developed in the Nile Delta. This expanded the habitat for the snail species that is required to sustain the complex life cycle of the parasite, and also increased human contact with infected water. Humans acquire infection when they come into contact with water and subsequently the parasite, which, in an early stage of its development, burrows into intact skin.

During the height of the European colonial era, in the late 19th and early 20th centuries, scientists from several European countries and Japan competed vigorously to determine the life cycle of the parasite, a critical step towards preventing infection. The Japanese discovered the parasite's life cycle in cattle. The British team working in Egypt then used this information to demonstrate how humans become infected. This led to a focus on snail control to prevent the disease, but it was largely unsuccessful.

Schistosomiasis leapt to American and international attention during World War II when thousands of American troops became infected during the invasion of Leyte.

U.S. researchers were concerned that returning troops would introduce the disease, spurring accelerated research in this country. While in the immediate post-war years only Egypt, Brazil, Venezuela and China assigned high priority to the disease and initiated national control programs, schistosomiasis existed and spread in many regions where it received less attention than more obvious killers such as malaria.

By the 1970s, when the TDR Program was established, the scientific and public health communities had been through several cycles of elation and dashed hopes from various efforts to eradicate disease; the cycle was then in its optimistic phase. The cycle first began early in the twentieth century when the Rockefeller Foundation established commissions to eradicate hookworm worldwide (1907) and yellow fever in the U.S. (1915); both failed and diminished the popularity of eradication efforts over the following three decades. But, following the successful elimination of malaria from specific regions and the development of a stable vaccine for smallpox, the notion that disease eradication was possible came back into favor with public health practitioners. When, in the mid- to late-1950s, the WHO adopted the goals of global malaria and smallpox eradication, optimism for eradication efforts was high (CDC 1993).

While the vaccine-based smallpox eradication campaign concluded successfully in 1977, WHO's malaria eradication effort failed due to a host of factors, including mosquito and drug resistance and rising costs. WHO's failure with malaria—at a cost to its funders and constituents of \$1.4 billion over ten years—renewed the climate of skepticism for eradication campaigns.

It was not surprising, therefore, that in the early-to-mid-1970s the view of most schisto experts was that multi-faceted interventions were needed to control schisto and its transmission: The reigning approaches included drug treatment, snail control and other interventions to decrease water contact and to diminish contamination of potentially infective waterways. Recognizing the immense resources required to control schisto through these approaches, however, some international program architects of the time favored a “silver-bullet” approach. Highly focused on a “single solution,” such

approaches were intended to balance the competing needs of effective health care provision and resource constraints.

The 1970s also witnessed the emergence of the field of molecular biology and its application to immunology. The scientific potential afforded by these techniques (hybridoma, monoclonal antibody and recombinant DNA) created a climate of “immunologic exuberance”; although the field was just getting underway, optimism was high that these advances would help lead to vaccine development over time. The optimism for a schisto vaccine, at the earliest stage of the TDR Program, arose within this climate as well as from previous, more-or-less empiric successes in developing effective vaccines for bacterial and viral diseases, such as DPT, polio, and others.

Ultimately, however, vaccine technology became viewed as the “silver-bullet” to control schistosomiasis. The necessary factors seemed within reach, given the known characteristics of the disease, and a reasonable “scientific likelihood” conferred by the new technologies. A vaccine was viewed as preferable, given the complex nature of alternative approaches to control (such as eliminating the intermediate snail hosts for the parasite before it infects humans).

b. Scientific and Historical Context of the Schistosomiasis Program

Ever since scientists learned that snails were an essential part of the life cycle of the parasite, efforts to control schistosomiasis have been mounted. The early decades of control focused on devising methods to kill snails in their aquatic habitats. While it seemed reasonable that snails were the most “exposed” part of the parasite’s life cycle, and vulnerable to attack, decades of research revealed that complete elimination of snails was virtually impossible in most areas where the disease was common, and that the cost and ecological consequences of repeated application of molluscicides limited their usefulness as a control tool. Furthermore, snail control had no immediate impact on disease because the adult parasites are long-lived in the human host, and interruption of transmission could require years, if not decades, of continuous control of the snail (the

intermediate hosts). Research on biological control of snails yielded few if any practical applications. Drug therapy research did generate anti-schistosomal agents, but until the early 1970s their use was limited by severe, potentially fatal side effects and the need for multiple doses (usually 12) administered by needle. Scientists targeted alternate points in the parasite's life cycle for transmission interruption. These included preventing the contamination of fresh water bodies with excreta (sanitation), preventing contact with potentially infective water (provision of safe water supplies, health education) and eliminating snail breeding habitats through engineering approaches. While in theory these interventions could contribute to control, and generate knowledge that would benefit other diseases, none by itself could be expected to interrupt schisto transmission.

A number of organizations were active in schisto research around the time that the Foundation's program was created. Some (e.g., the East African Institute for Medical Research in Tanzania, part of the British Medical Research Council) were vestiges of the colonial era, and maintained a strong schistosomiasis research program. Similar groups existed in or were linked to other European countries including France, Belgium, Germany and Denmark. Other centers of schistosomiasis research existed in countries that recognized the disease as an important public health threat: Egypt, Philippines, Brazil and China (which ultimately achieved widespread control). Sizeable schisto control projects were also carried out in Syria, Iraq, Iran, Ghana and Tanzania. In addition to China, a few countries that underwent rapid socioeconomic development enjoyed successes in eliminating or controlling schistosomiasis; these included Israel, Japan, Venezuela, and Puerto Rico.

In the early 1970s the international public health community recognized that malaria, schistosomiasis, and other tropical parasitic diseases were worsening in many developing countries, especially in sub-Saharan Africa. The Special Programme for Research and Training in Tropical Diseases (WHO/TDR) was formally created in 1975 to

target research on six tropical diseases¹. Schistosomiasis was considered second only to malaria in significance within this program.

In the United States, the network of schisto researchers and funders was small. Pockets of schistosomiasis research expertise were found in the military, the CDC's San Juan Laboratories in Puerto Rico, and in several academic institutions (mainly Harvard, Tulane, Case Western, and Johns Hopkins). The Rockefeller Foundation had supported a large schisto project in St. Lucia that was designed to assess alternative control strategies. Dr. Joseph Cook conducted research for the St. Lucia project prior to moving to the NIH from where he was ultimately recruited to direct the Clark TDR Program. Similarly, Dr. Ken Warren, then at Case Western Reserve, and an early advisor to and grantee of the Foundation's Program, subsequently went to the Rockefeller Foundation where he directed the *Great Neglected Diseases of the Developing World* Program. Despite this scattering of human and financial resources, funding for schistosomiasis was quite meager relative to that for malaria and domestic health problems. Furthermore, with the exception of Rockefeller's applied research in St. Lucia, no organization was clearly identified as a focal point for schistosomiasis research.

c. Initial Goals and Objectives of the Schistosomiasis Program

After determining that one program would focus on the Developing World, EMCF sought to define its niche according to the following standard: Given the myriad problems and enormous population at risk, which problem presented the best opportunity to make a meaningful, rather than marginal, impact? Thirteen areas of opportunity were identified and explored on a preliminary basis; the three most consistent with this criterion were emergency relief, craft development, and tropical disease research².

¹ The formally titled UNDP /World Bank/WHO Special Programme for Research and Training in Tropical Diseases, was established to facilitate the intensification of research on tropical diseases, as well as to promote and strengthen research and training in developing countries. It was unique in that, as an extrabudgetary program, TDR was not dependent on the WHO Assembly for funding; it received broad-based support from multilateral funders, and, in contrast to other WHO programs, was also a grantmaking body.

² Other areas of opportunity explored for the Developing World Program included: literacy, population and family planning, agriculture, job creation, housing and human settlements, management and management systems, health care delivery, nutrition, and the environment.

Among these three, exploration suggested that tropical diseases would provide the most dominant area of opportunity for several reasons. In 1974, more than one billion people were affected by *at least* one of twelve prominent tropical diseases, and data from WHO, NIH and CDC indicated that only \$21 million per year were expended annually worldwide on tropical disease research (IDAU 1973). Ten major funders contributed to a broad spectrum of research interests within the field of tropical disease research, but there was no critical mass of activity or funding in any one area. Of the twelve “prominent” tropical diseases, schistosomiasis was identified as one that was prevalent in many areas and becoming more widespread (in part, concomitant with development efforts), and had garnered few resources (approximately \$3 million per year) (IDAU 1973). Thus as the largest, single private funder of schistosomiasis research, Clark’s entrée into tropical disease research was substantial in terms of credibility and financial impact on the field.

During its first year (FY 1973-'74), staff established three broad objectives toward the goal of global schistosomiasis control established for the nascent program.

- 1. Determine the impact of the disease to influence major funding agencies and the government to carry out research and control programs in schistosomiasis, by supplying them with appropriate economic and social data that show the importance of the disease to development and well being;*
- 2. Determine whether and how immunity occurs in man as an important first step in determining whether the development of a vaccine is feasible; and*
- 3. Increase the quality and effectiveness of control efforts with available medicines and counter measures short-term to make control more economically feasible and more effective, and to develop new and better methods of control longer-term.*

d. Schistosomiasis Program Narrative

During the Program's first year, in conjunction with "selected scientists" and WHO representatives, staff refined the strategic plan and presented it for further development to invited scientists at a workshop in St. Lucia, the site of a Rockefeller-funded schisto control research program. The plan sought to characterize the "landscape" of tropical disease research and the funding sector supporting it; it also aimed to define a unique role and leadership position for the Foundation. Workshop participants were challenged to consider and "borrow" the tools and techniques of management consulting from the private sector by defining program goals in terms of time, desired results, and financial commitments. As Dr. Hoffman recently described, "*I came to the workshop with problems I wanted to solve, and asked workshop participants to help solve them.*"

Participants included experienced and field-seasoned researchers, and a small number of promising young investigators keenly interested in immunological aspects of the disease. Convinced that a "systems analysis" approach, borrowed from the corporate world, was the most effective way to undertake research directed at disease control, Dr. Hoffman sought consensus among the participants regarding research goals and objectives. A vitally important consequence of the strategic planning process was the enthusiastic "buy-in" by the participants, providing them, from the beginning, with a sense of ownership and deep involvement.

By late 1975, the Program plan was in its second iteration. Its mission, justification, goals and objectives, and means to achieve them had been rendered more precisely by Dr. Lehman (Lehman 1975). At this time, the Program Plan for the Developing World identified its primary long-term goal as the "*achievement of effective control of schistosomiasis and its elimination as an important disease.*" This would be achieved by developing the means to control schisto and stimulating and assisting governments and key agencies to "*undertake schisto control on a systematic and meaningful level.*"

Explicit recognition of probable constraints to schisto research by a broad range of experts informed and defined the program strategy. In the 1975 planning document, Dr. Lehman set forth a basic strategy and a scientific agenda that had four key components.

First, Dr. Lehman recognized that EMCF must create a “broad-based, multidisciplinary attack” on schisto because scientists considered it unlikely that any one method could effectively control the problem, nor that any single agency would have the commitment, planning and resources to coordinate the necessary control efforts. By virtue of its commitment, EMCF created a leadership position for itself in this broad-based attack that demanded significant interaction with diverse funders, governments and other parties acting to advance research and control efforts. TDR took on the roles of communicator, organizer and convener of these groups.

The second strategy component, to use the Foundation’s power and authority to influence (“leverage”) the field, followed naturally from the establishment of the Foundation’s role with its “partners” in schisto research and control. During the formative period from 1973 through 1974, staff intentionally sought to co-opt the scientific community by bringing leading research and control experts into the planning process. This served multiple interrelated purposes. It provided the Foundation with access to the expertise it needed, stimulated greater interest and thus momentum in the field, and exposed participants from research and control to the importance and benefits of the strategic planning process borrowed from the private sector. Policy manipulation, as it affected the control community, was articulated as another important aspect of the Program’s leveraging strategy. Staff recognized that the role of catalyst fell more naturally to WHO, but that “*a host of severe constraints*” prevented WHO from achieving that position (Lehman 1975).

The strategy’s third component was comprised of a formal mechanism to inform the field and the Board through an annual review of research progress. This included new trends in science, progress in disease control, and research priorities. Scientific

advances were to be reflected in an updated program plan that would constitute the basis for the Board's decisions. In addition to being an endpoint in itself, the review process would serve to bring together a diverse group of researchers and encourage the exchange of ideas between those involved in basic research and in control, and, in doing so, would help counteract the fragmentation recognized to occur naturally in such a diverse field.

The fourth strategy component, basic provision of services to the field, reflected the need for a single leader among schisto research organizations. Viewed as most prominent among the "services," was the granting process, providing \$4 million over the first two years to a field whose total budget was approximately \$6 million during this same period. The strategic plan for schistosomiasis was another "service," guiding applicants by supplying both current knowledge and identifying gaps in the knowledge base. This strategic plan was envisioned as both a prototype product and process for other, future, TDR disease efforts. Organization and sponsorship of technical workshops for laboratory and field-based control investigators was a third service provided to the research community. The Foundation also functioned as an information clearinghouse, sponsoring compilation, library-building and dissemination efforts.

Over time, strategic planning and co-option of the scientific and relevant political communities were accomplished systematically through the use of workshops, Task Forces and Advisory Committees (to be discussed in detail). Additionally, select grants were made to pilot test area-specific control strategies. The options posited by Lehman created the opportunity for engagement on a broader but less controllable level. In the end, the Program opted for tighter, more focused interaction with international agencies and governments, and in doing so, was possibly able to wield greater influence and control than would have been likely operating in situations with a greater number of partners.

In the November 1975 Program Plan for the Developing World, Dr. Lehman identified six objectives to pursue the means to control schisto, the ultimate goal. The first four further defined the principal areas of research: (1) determine whether immunity

exists in or can be induced in man and whether human schistosomiasis can be prevented or ameliorated by immunological means; the long-range objective was development of a practical vaccine; (2) develop safe, inexpensive, easily delivered, curative and prophylactic anti-schistosomal drugs; (3) increase the effectiveness of other control measures that interrupt or reduce transmission of infection to prevent development of clinical disease; and (4) determine the economic and public health significance of schistosomiasis.

The fifth objective was to “*present and update a plan for research (the Strategic Plan for Research on Schistosomiasis) which systematically addresses the four research objectives above.*” The initial Strategic Plan was revised into a June 1975 edition that, in its preface, states “*The plan provides a basis for all decisions by the Foundation on grants and contracts. It provides a framework for prioritizing research in an area where the need greatly outstrips resources.*” This (second) edition was also the first to incorporate target dates of benchmarks for research-related decisions, actions and products.

A final, sixth, objective was to “*develop advances in national and international policy and funding; long-range objective is national, regional or global control schemes.*” While broadly addressed in Chapter VIII of the Strategic Plan (Global Control), these broader objectives were not strictly part of the plan.

The use of strategic planning to guide research on biological processes and disease control was a new and, for some, radical innovation. According to Mr. Emery, “*Don Hoffman thought that it was shocking that medical research was being carried out as a cottage industry. Our goals were to address the needs of the underdeveloped world, and to try to bring a scientific focus on diseases affecting the underdeveloped world... We were attracted to a strategic planning approach to disease control on three levels. It would help focus on relieving the misery of people suffering from tropical diseases. Second, we wanted to draw more attention by the western scientific community to tropical diseases. And, in science, where so much had been accomplished on vaccines and disease control, why should the scientific community be blind to the strategic NASA*

approach? We decided that adopting a NASA-type planning approach would be a useful way to go...When we encountered barriers, we took an entrepreneurial approach to removing those barriers. It was 'seat of the pants'." NASA had utilized a highly targeted and specific engineering plan to propel its space exploration mandate using extant technology. The task was to organize and integrate it to achieve specific objectives, and to do so within a precise time frame.

As Mr. Emery continued to explain, *"At the start of the Schisto Program, and for about the first two years, we were supporting traditional vaccine research techniques and didn't anticipate that the science would be so rapidly evolving with molecular biology techniques. When the sunburst of molecular biology did occur, we may have, or should have, reassessed our plans to account for the likely changes that this new science would bring."*

Biomedical research did differ somewhat in that all the necessary technology for the molecular biological approach to vaccine development did not yet exist. Instead, contemporary funders supported investigator-initiated research that was scientifically rigorous and considered to address important questions. The Program's "directed research" was considered by some scientists to be counterproductive and infeasible. According to one informant, *"The idea that you tell anyone what to research was anathema."* The outcome of scientific experimentation, reasoned this informant, can not be anticipated. According to one skeptical grantor, *"Donald Hoffman believed that with good management, one could accomplish anything in research."*

One NIAID official recently indicated that *"in the early 1970s, NIAID was not working on a schisto vaccine. We decided science didn't know enough about the parasite's effects on the host immune system and whether protective immunity could be conferred. So, NIAID concentrated on basic research that might help guide a vaccine approach...The NIH philosophy has been that investigator-initiated free-ranging research should get us farther down the road, since you never know where the advances will come from. For example, the monoclonal antibody technique came from research on*

multiple myeloma. The researchers were interested in cancer. They didn't set out to develop monoclonal antibodies. We decided the most unproductive way to work toward a vaccine was strategic planning, because there was no room for serendipity and chance."

How then did the staff and Board decide that these six objectives were realistic within the time and resources anticipated? Planning documentation from 1973 states that *"entry into this area will require a commitment of at least 5 to 10 years."* From recent interviews it appears--at least in retrospect--that few Board members, staff, advisors, collaborators or grantees actually expected the vaccine-related objective to be met within the timeframe envisioned. Rather, the objective was often viewed as something to be achieved in the distant future. For instance, according to one Board member, *"Molecular biology burst onto the scene. But, there was no indication provided at the outset that any vaccine was possible. So, scientific optimism drove it."*

This was confirmed by Dr. Hoffman. *"There was no scientific indication, evidence, or experience to date that a vaccine was feasible within 5 to 10 years, I didn't think development that soon was feasible. Rather, I was trying to create an environment within which vaccine research could progress, flourish. By getting immunologists and molecular biologists to think about schisto and adapt their work to the field, we could help create that environment."* He added, *"Implicit in our early plans were to get good people...immunologists who had not previously worked in schisto ... to adapt their interest and work to schisto and thereby transform players and the thrust of the field."*

Dr. Lehman re-emphasized the long-term nature of the challenge in a 1976 discussion with the Board. *"The number of basic research questions is formidable, and will require considerable, long-term investment on our part."* But long-term to Dr. Lehman meant that *"development of an effective vaccine was as much as ten years away,"* as he wrote in his 1978 Program Update. He was more optimistic than most.

But not more optimistic than a newly trained scientist recruited into the field by its promise and its importance. Looking back on that time, the scientist recently said,

"We were very naïve back then. We figured that as soon as you identified an antigen you would be able to make a vaccine. Everything that had worked to that point had been straightforward such as measles, mumps., rubella, pertussus, smallpox, polio."

As Dr. Cook recently commented, *"We had very definite goals and expectations to do certain things by a certain time. Not all were successful...As the process evolved, we got more explicit in honing objectives and strategies...Immunologists would tell us that a vaccine was about five years away. The problem was, they told us that every five years."*

Once established, the strategic plan was first reevaluated in 1976 by the staff who determined that the *"basic directions and priorities [are] sound, revision [is] unnecessary."* While the periodically updated strategic plans for schistosomiasis research did contribute importantly by involving scientists in the planning process, and in building partnerships based on shared interests, they were unsuccessful in forecasting scientific progress in the basic research domain of immunology and vaccine development. Anticipation of scientific progress in that domain was greatly influenced by the enthusiasm and inherent optimism of talented, goal-oriented scientists who firmly believed that with adequate support, questions could be answered and technical obstacles overcome. As one investigator commented, *"Scientists were not too sure how serious the Foundation was in trying to be doing a strategic plan. Most scientists probably didn't pay too close attention. Most were immunologists or parasitologists rather than people who really understood the steps along the way and places that get bogged down in vaccine development."*

Evidence also suggests that the role of the strategic plan in guiding progress of the Program was less transparent to some Advisory Committee members and scientists in the field. One informant recalled being *"both impressed and worried with the strategic plan's inordinate detail."* As a result, strategic planning was perceived as far more successful in guiding applied as opposed to basic "bench" research. In this way, the strategic plan served the dual purpose of a framework and unifying "umbrella" document.

It appears that the Clark Foundation's approach to strategic planning may have influenced that adopted by the newly-created (1975) WHO/TDR Program. *"Unlike other Scientific Working Groups of the Special Programme, schistosomiasis research throughout the world in recent years has been oriented, if not actually guided, by the 'strategic plan' for schistosomiasis research developed by the Edna McConnell Clark Foundation"* (WHO/TDR 1980). Although alternate sources of the genesis of strategic planning at WHO/TDR were offered by some informants, most acknowledged Clark's role. In either case, there is broad agreement by WHO/TDR officials that strategic planning has made a vital contribution to biomedical research designed to create and improve tools for control of tropical infectious diseases.

Just prior to Dr. Lehman's death, the Program Plan was reviewed by leading bench and field scientists at a 1977 meeting in Bellagio, Italy. A report of the proceedings, entitled "Optimal Strategies for the Control of Schistosomiasis," was published a few months later. In a good example of effective exchange between scientists with differing perspectives of schistosomiasis research and control, meeting participants resolved that the Foundation should stay in schisto research and provided recommendations on how best to proceed.

Bellagio meeting participants concluded that major gains in control of schisto could be made with current technologies in major endemic areas. Maintenance of control in most endemic countries, however, and establishment of new control programs in less-affected countries, would require the development of less expensive modalities that needed little monitoring.

Thereafter, a five-member advisory committee convened in June, 1978 to consider questions posed by Foundation President Dr. Jack Coleman regarding the optimal path for the Schisto Program over the next few years. Committee members concluded that it was in the Foundation's and field's best interest to remain in schisto. Follow-up recommendations from the Bellagio workshop focused on mechanisms to strengthen the existing program by adding a technical advisory committee to work with

staff on various aspects of Program evolution, including strategy and funding mix for the four existing sub-areas of immunology and vaccine development, biochemistry and drug development, control and impact. As Dr. Coleman recently reflected, *"Maybe it was a product of my ignorance or arrogance, but I didn't find it [the task of conducting an international program] daunting. At the time, about the only other funder was Rockefeller. I thought, 'Hey, this is probably worth doing.' I don't frighten easily."* Based on recommendations provided at the Bellagio meeting and thereafter, Dr. Coleman selected Joseph Cook, M.D. as Program Director. Dr. Cook was recruited shortly after his arrival at the NIAID and joined the Program in November, 1978.

e. Schistosomiasis Program Processes, Operations and Tools

Throughout the Program, the grantmaking tools used to carry out the directed efforts to develop a vaccine, create improved drugs and more effective control measures varied for each sub-area and continued to evolve with experience. Grants for the fourth objective, determining the economic costs and public health significance of schisto, never got underway as the difficulty of the task became realized. Instead, grants were awarded to explore various policy-related questions pertaining to product cost-effectiveness, cost-benefit, production and marketing.

Grants for immunology and vaccine development dominated in terms of total funds and number of grants throughout the Schisto Program (\$16.5 million versus \$10.1 million for epidemiology and control and \$5.7 million for drug development; in addition, the average immunology grant was 54% larger than grants in the other two subprograms). For the first decade, 1974 to 1983, funded applications for vaccine research were submitted by leading researchers from the several major academic centers in the U.S., England and France, where this work was largely concentrated.

In 1983, as the Foundation began to narrow efforts as a prelude to exiting the field, the TDR Program initiated a competitive grants program narrowing the focus of vaccine-related research grants to molecular biological techniques. Applications were

either for using molecular biology techniques to identify protective antigens or for using recombinant DNA methods to produce adequate quantities of these antigens. According to Dr. Cook, the process also provided an opportunity to bring new researchers into the field.

Six of 18 invited applicants were funded in 1983, based on the criteria of scientific merit and chance to succeed. Additional competitive rounds were held in 1985 and 1987, the year that the Foundation moved the process outside by providing a grant to Vanderbilt University (Dr. Daniel Colley) to establish a Task Force to coordinate and oversee vaccine research as part of the Foundation's schisto exit strategy. Researchers were told that future support would be for the Task Force, not individual research projects. Through this ten-year competitive grants process, the Foundation was able to support closely-related research on several promising vaccine candidates, and stimulate interaction among grantees while the Foundation's efforts were winding down. At the time the Program ended, three potential antigen candidates had been identified, one of which was being tested in primates.

Workshops became an integral part of information exchange among vaccine researchers, with \$116,000 provided over time for both self-administered and institutional grants to convene the sessions. Following an initial workshop jointly convened with WHO in 1974, the Foundation funded a self-administered grant in 1980 to convene a workshop on immunology related to developing a live, attenuated (weakened) vaccine. (Self-administered grants were a way to maintain direction and control within the Foundation, rather than acting through a grantee who would have broad discretion.) Four workshops funded by grants to universities followed from 1981 through 1986. The subjects included vaccine immunology, an "antigen lab" workshop, molecular biology techniques, and "progress reporting."

Grants to develop improved drugs supported a variety of interrelated activities, from research to policy development, and patent to liability protection. Addressing market-constraints, the Foundation became problem solver and entrepreneur. Drug

development tools essentially reproduced the process that industry used to search for promising drug agents. These included \$523,000 in support to Parke-Davis (later Warner-Lambert/Parke Davis) between 1974 and 1979 to prepare chemical compounds that might lead to development of drugs that were safer, more effective, and easier to use compared to those then available. Because two of Parke-Davis' products had been found to be carcinogenic in mice, grants to academia supported evaluation of simple biologic systems for detecting potential carcinogenic effects, while other academic grants supported testing of compounds in mouse and monkey models.

Contracts were used as early as 1979 to obtain legal assistance in patenting products to gain market protection for those developed. Patents were initially filed for a diagnostic radioimmunoassay test for antigen detection developed by Case Western Reserve University grantees. Also patented was a metabolite of the drug niridazole, originally developed by Ciba-Geigy, which was found by Case Western grantees to have immunosuppressive activity. The metabolite was then licensed to Sterling Drug. Contracts for legal assistance gave way to a self-administered grant to handle this work internally as the number of potentially patentable products increased over time. The Foundation's patent practice preceded the Bayh-Dole Act of 1980, which sought to advance market availability of federally-supported products of research by requiring academic grantees to take out patents on their potential products, so that industry would be more likely to develop them further and market them, or risk losing intellectual property rights to the government. Prior to the Act, NIH had discouraged its grantees from seeking intellectual property rights to products financed by public funds.

After the drugs praziquantel and oxamniquine became available in 1982 for human use in treating schisto, but at high cost relative to developing country health budgets³, a new tool was invoked. The Foundation awarded grants to try to create a new process for synthesizing praziquantel which had been developed by the German pharmaceutical company Bayer under license from Merck. These grants were not

³ In 1978, Praziquantel retailed for \$6.50 per 600 mg dose; discounted pricing for WHO in 1981 was 90 cents per dose (Reich 1997). Since that time, the price has dropped substantially and is now at about 10 cents for a 600 mg. tablet (Cook 2000).

successful. But, some years later, a Korean pharmaceutical firm, Shin Poong, devised a means to synthesize the drug that differed from that used by Bayer. Because Bayer had patented the production process rather than the compound itself, Shin Poong was able to compete directly against Bayer with its newly synthesized product for the retail and public (government) sector markets. For example, in Egypt, Shin Poong licensed its product to the Egyptian International Pharmaceutical Company which began to market the drug in 1987, resulting in significant price declines in that country (Reich 1997).

In light of the availability of praziquantel and oxamniquine, essentially single-dose oral drugs⁴, the Program phased out of drug development and grant emphasis turned to the systematic improvement of control strategies using the available drugs. For a decade beginning in 1980, various institutions received grant funds to (1) measure the effectiveness of mass chemotherapy using oxamniquine; (2) test the effectiveness of praziquantel in controlling *S. japonicum* and *S. haematobium*; (3) study the effectiveness of various combinations of drugs; and (4) expand the use of national drug treatment programs.

Also during this time, grants were provided to academic institutions to develop inexpensive, easy-to-use field tests for diagnosing urinary schisto. These included tests for immunodiagnosis of schisto, the GIST (galactosidase immunosorbent test), blood tests, a diagnostic test kit for *S. haematobium*, and ultrasound for diagnosis of secondary liver fibrosis in people with schisto. In addition to developmental grants, the Foundation supported a conference on immunodiagnostic tests, and research to isolate antigens leading to diagnostic methods. One of these products, a Case Western immunodiagnostic technique for field use, was patented.

Grants were used also to determine ways to overcome market obstacles to schisto drug development, vaccines, and diagnostic agents. These included a 1978 survey of

⁴ Recommended treatment protocol for *S. haematobium* and *S. mansoni* is 2 doses (20mg/kg) in one day; *S. japonicum* and *S. mekongi* require 3 doses (20 mg/kg). *S. mansoni* may be treated with single dose (15mg/kg) oxamniquine or in N/E Africa one (20mg/kg) dose x 3 days. Source: Sanford Guide to Antimicrobial Therapy, 1998.

U.S. drug companies on their research on drugs and vaccines for use in tropical diseases and barriers to this work. This survey was extended later to European companies. A 1979 study explored the potential for developing a purchasing cooperative among developing nations to put them in a better bargaining position regarding drug charges, and a grant-supported symposium was held to discuss this possibility. Additional studies examined drug marketing, funding and distribution practices, and cost-benefit and cost-effectiveness assessments of drugs and vaccines. To prepare for potential vaccine development and distribution, a 1988 grant was awarded to identify and evaluate the capacity of companies in Brazil and Egypt, where schisto prevalence was high, to produce vaccine. Companies' capitalization, existing product lines and market capabilities were analyzed.

From the beginning, grant efforts were accompanied by communication activities designed to keep scientists in the field informed and involved. Communication grants began in 1974 with an anthology of schisto research progress and a review of schisto control projects. These became the basis of schisto libraries in medical schools and ministries of health in infected areas. Grants supported publication of journals (*Tropical Doctor*), and of research results, first in the *Schisto Packet* and later in the *Schisto Update*. The latter was cited by many informants as useful, particularly in the field where it was difficult to access the literature. The Program also supported a PBS film on schisto, and more than nine scientific conferences and symposia for basic and field researchers. Additionally, the Foundation supported educational courses on parasitic disease, primarily schisto, from 1979 to 1991 through grants to the Marine Biological Labs. The Foundation did not, however, seek to use communication systematically to develop a more committed public constituency for schisto research, or for bringing down the price of praziquantel. Commenting recently on this, Dr. Coleman explained "*The Clark's didn't want publicity. Trying to make a case about the need for lower drug prices probably would have been unacceptable at the time. I did bring in a director of communications, but this was to help grantees get their stories out.*"

This interrelated and flexible use of a broad array of grantmaking tools that were tailored to achieve specific objectives enabled the Program to direct the \$32 million devoted to schisto in a highly strategic fashion. The Program combined industry support for compound development with competitive support for academic research targeted to drug and vaccine development objectives. Self-administered grants to carry out patent protection efforts helped to foster the ability to bring products, particularly diagnostic tests, through development and to market. Funding for academic researchers and for research Fellowships, combined with educational courses provided by the Marine Biological Labs, helped to attract and train scientists in the field. A Task Force to oversee and coordinate vaccine work, workshops for investigators to discuss common problems, conferences and symposia to address research and policy issues, and research updates for the field fostered efficiency which contributed to the systematic pursuit of vaccines, drugs, diagnostic agents and other means of control.

f. Schisto Exit Strategy

General discussion of potential future directions for the TDR Program, first discussed at the 1977 Bellagio meeting and a 1978 Advisory Committee session, emerged again during the 1979 review process. Pursuant to discussions at several prior Board and Advisory Committee meetings, the Board decided in September 1981 to phase out the Schistosomiasis Program.

The question of an exit strategy for the drug development objective, now that praziquantel and oxamniquine were marketed for schisto treatment, was first raised by a Board member at the March 1981 Advisory Committee meeting. The Foundation diminished funding for drug development that year and ceased it altogether in 1983, except for three grants to develop a new, simplified process to synthesize praziquantel.

In an August 1981 pre-Board memorandum, Dr. Cook advised President Coleman that *“our rate of exit from the schistosomiasis field should be determined by our progress toward initiation of control programs....”* Dr. Cook also indicated that while the (basic)

research component had not yet yielded any “*knowledge that could be translated into field application,*” it had produced “*striking new knowledge*” [in immunology] that “*may provide the long-term definitive answer to control.*” Dr. Cook also pointed out that Clark support had clearly “*developed a critical mass of first rate investigators...this solid foundation is one we should and are examining carefully before abandoning further support*” (Cook 1981). As Dr. Coleman recently reflected, “*I was fully prepared to go slow in this case. There was an identifiable goal, to develop a vaccine. As long as there was hope, that persuaded me that we were right to stay the course.*”

Following the Board’s September 1981 decision to phase out of schisto, the Board requested that TDR staff explore other potential opportunities for the TDR Program. In response, staff initiated a series of exploratory grants using 10% of the schisto funds that the Board reallocated to exploratory investments⁵. Topics included acute respiratory infection (ARI), amoebiasis, blindness prevention, leishmaniasis, refugee and migrant health, and toxoplasmosis. Upon examination by staff and the Advisory Committee, it became evident that none of the diseases under exploration met the Foundation’s criteria: As protozoal agents, leishmaniasis and toxoplasmosis were inconsistent with the Foundation’s experience with schisto and thus did not provide the type of niche to which the Program aspired. Amoebiasis and ARI, given their multifactorial nature, had the potential to become too diffuse. Refugee and migrant health, staff concluded, received support from an array of public and private entities, some of which were more strategically positioned than the Foundation to make an impact.

In November 1983, the Board approved a plan for gradual withdrawal from schisto and a plan for the development of a program to control two major infectious causes of blindness: oncho and trachoma. Archival and interview data indicate that the withdrawal plan was designed to support the conclusion of important ongoing research

⁵ Exploratory grant clusters: ARI: 11 grants between 1982-86; 8 in 1983-84, 1 in 1982, 1 in 1986.
Leishmaniasis: 1 grant, 1982.
Amoebiasis: 5 grants, 1982-83.
Blindness Prevention Opportunities: 1 grant, 1983.
Refugee /Migrant Health: 2 grants, 1980 and 1982 respectively.

while preparing the schisto research community for the eventual phase-out of schisto funding. By 1985, the exit strategy for the Schisto Program—which represented 39% of the TDR budget that year--had become more refined, and specific goals for the Program were identified that would signal the conclusion of the Program’s three main components. In Epidemiology and Control, the Program would support tests of specific control strategies and facilitate the transition of pilot control efforts into public health activities through 1988. Staff recognized two salient issues were residual to the schisto work: drug resistance and drug delivery. Although praziquantel and oxamniquine offered a substantial advance in disease control efforts, delivery was still an obstacle in areas of high endemicity requiring annual retreatment.

Foundation President Peter Bell said in a 1987 Advisory Committee meeting that the *"Trustees decided to withdraw from schisto slowly, but we were clear now that we have a responsibility to stay with it in a more narrowly focused way...the Foundation feels some responsibility to maintain a role in control of the disease, since we are not sure that we'll be successful in developing a vaccine."* Asked recently about these statements, Mr. Bell said, *"Increasingly we doubted we would be successful in vaccine development. But we decided to stay in the field, given the need to bring the work on a possible vaccine to an orderly conclusion and the new possibilities from advances in epidemiological research and lower-cost drug therapy. We decided it would not be responsible to cleave it off, so we decided to attenuate instead."*

During the withdrawal period, support in immunology and vaccine development would be provided to identify and test antigen candidates through 1987, at which point a decision would be made on whether to pursue one or two vaccine candidates for further development. In communication, the *Schisto Update* would continue through 1989, if “still essential.” In an effort to maintain momentum and solidarity within the grantee community, the Schisto Vaccine Task Force (SVTF) was established at Vanderbilt University through Foundation support in 1987. This support continued through 1991, at which time the Task Force and its funding were transferred from Vanderbilt to WHO where it was supported through 1993. The rationale for the transfer was that as WHO

would be ultimately responsible for the delivery coordination of any successful vaccine, *“it made sense for WHO to assume greater responsibility for guiding future efforts at vaccine development,”* according to the Program Plan. Despite exit plans, staff proposed as late as 1990 a vaccine research agenda for the Board’s consideration. Staff indicated the need for a review of the current approach to advancing immunological research on schisto utilizing recombinant antigens, or whether *“a different pathway, if any”* should be pursued.

Advances in the commitment to and application of scaled-up schisto control efforts had met resistance within countries. As of 1990, only Brazil and China had implemented national control programs. In 1988, staff reported that pilot control programs in Kenya had demonstrated that the treatment of school age children was the most cost-effective approach to controlling morbidity from schisto. In response to this opportunity, the TDR Program staff changed tactics. Instead of total schisto withdrawal, staff sought to apply the geographic-centered approach that had been adopted by the Foundation as a unifying theme among domestic programs. This geographic-centered approach was also a means of building on WHO’s concept of regional control. It is unclear from available documentation why national control efforts did not make it onto the “agendas” of afflicted countries, nor how a regional approach might succeed where a national one had not. Staff also suggested that an expansion of integrated parasitic disease programs might offer an alternative means to promote schisto control.

The “geographic-centered approach to funding” adopted by the Foundation in 1991 was used to focus on control efforts in two distinct locales, East and West Africa. According to Peter Bell, *“I was concerned about the disjunction between domestic and international programming and thought a geographic focus could help to bridge the differences, with an aim to move toward control of certain infectious diseases or health-related problems. But, this would have implied something different from our science-based activities, and it was difficult to try to make that shift.”*

At the same time, the Task Force for Child Survival in Atlanta was planning an expanded school-age child chemotherapy program aimed first at schisto and secondly, oncho and intestinal helminths. The Task Force's plan presented an opportunity for the Program to remain focused on schisto control while meeting the criteria for geographic-centeredness.

The schisto withdrawal strategy had been predicated on several assumptions: (1) that praziquantel and oxamniquine now filled the niche for a simple, effective chemotherapeutic means of control; (2) further investment in chemotherapy was no longer warranted except for treatments in the presence of resistant strains of schisto; and (3) WHO would and could carry the mantle for schisto vaccine research forward. Response from the field was mixed:

"In retrospect, we started too early on a vaccine; when [Clark] left the field, there was not a perception that the money wasn't well invested in vaccine research, rather that they needed to get out."

"We knew they would phase out; because Joe dragged his feet, we had time to adjust," but "we weren't prepared to find new funding; this was difficult because the pool of funders was shrinking...Clark's withdrawal was detrimental...[their] moral support was as important as financial."

[One informant] identified one misconception in the Foundation's approach: *"They believed that "someone else" would step in to support schisto [when they withdrew] but it was not the case. Although the European Union support for research linkages in Europe did emerge, this source offered no support for the U.S.-based investigators, nor a means for those Clark helped start to continue."*

[This informant] attributes this misconception in part to the *"corporate MBA-like assumption"* [by Dr. Hoffman] *"that foundations should change directions every 5-10 years; this may be true in the corporate world, but not in bio-medical research...Clark could not understand this."*

As one of the researchers attracted to the field primarily by the security that funding beyond that of NIH provided said recently, *"It came as a shock to the research community that foundations don't operate the same way as NIH. We assumed the program would go on forever. It was hard to accept that foundations go in with a goal to energize a research area (or maybe a product) rather than support research for the sake of research.....Rockefeller has moved out, MacArthur has moved out. So, now scientists realize that foundations aren't a steady bet for future career funding."*

A statement from another researcher voiced similar concerns: *“The withdrawal of a major funder is very destructive to the field and related fields ...[it] would be irresponsible to get out after 10 [years] because it plays games with scientists’ careers, it is a very capricious approach and ultimately discourages scientists...[a funder] must pull out in a gradual and orderly fashion.”*

One colleague from the foundation world saw Clark’s exit from schisto as a tribute to Dr. Cook’s integrity and respect for the research community as “client”: *“It’s a tribute to Joe that while two major funders abandoned the field—Rockefeller had no exit strategy--and thereby increased the pressure on Clark, Joe was able to stay the course and manage an exit strategy responsibly.”*

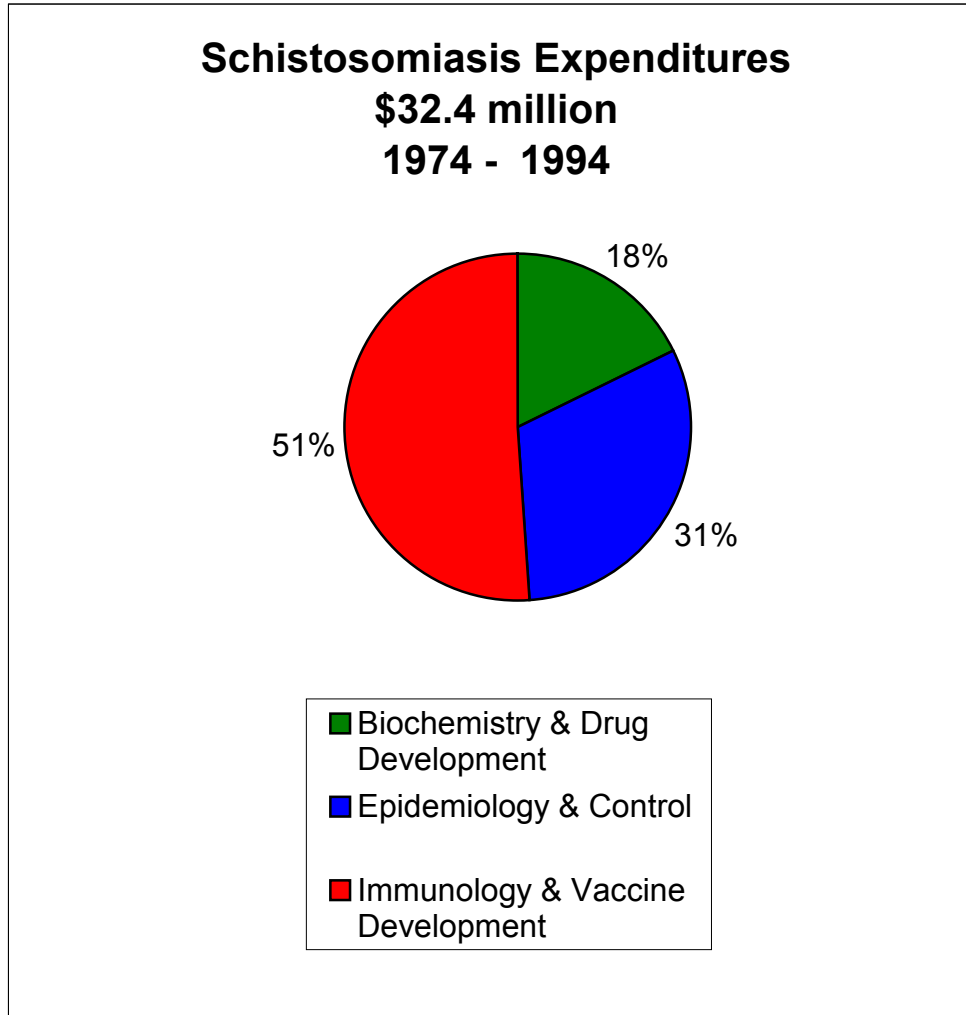
As Peter Bell reflected recently on the Foundation's withdrawal from schisto in a highly deliberate and slow way, *“Governments and foundations were turning away from interest in developing countries and international public health. We were more trying to keep a tradition of commitment alive, an increased sense of responsibility to stay with it. We believed that a steep and rapid decline in our grantmaking would be viewed as the withdrawal not only of financial, but also moral, support at a time when we had a disproportionate importance to the field because we were among the few private supporters.”*

While withdrawing gradually from schistosomiasis, the TDR Program segued into the trachoma and onchocerciasis fields. The Schisto Program was finally concluded in FY '94.

g. Schisto Program Outcomes

The TDR Schistosomiasis Research Program can be credited with an impressive list of accomplishments, both concrete and abstract. Although the Program did not meet its ultimate goals—to create a vaccine or drugs to control schistosomiasis—it fulfilled its self-appointed role as a catalyst in the field, in part by providing an estimated one third of all funding for schisto vaccine research (Barrett 2000). Outcomes included enlarging the cadre of researchers and stimulating the interest of international organizations and governments in schisto control; both were envisioned as “end products” and long-term investment opportunities within the broader schisto field.

Figure 2. Schistosomiasis Program Expenditures, 1974- 1994



The Foundation's investment nurtured the creation of an "invisible college" of schisto researchers who, individually and as a group, have brought the science underlying vaccine development and schisto control far since its inception. By becoming a secure funding source for more than a decade, the Foundation helped to attract new scientists into the field. *"EMC helped to get us interested. In the field, there aren't a lot of funding sources. So, the Foundation's funding was critical to making people feel like it's a solid career choice since there now were options apart from just NIH (Clark, MacArthur, Rockefeller, and now Burroughs Wellcome Fund). That contributed to a sense of security in selecting an area of relatively obscure interest. A lot of people directed their research toward schisto vaccine because of Clark. The Foundation had sound stature in the field, and that was very reassuring."* According to others:

"The Foundation ...encouraged first rate researchers to focus...at a time when few Foundations were. That has been a major contribution."

"The NIH hasn't taken up the role of trying to get young investigators into this field. NIH does have training awards in parasitology and a few might be in schisto, but no disease target in training grants to fill the void of the Foundation."

"There have been shifts [decreases] in funding, in part because people like Dan Colley have gone elsewhere [into government]. I believe new people are still coming in, but they are not being recruited into helminths at the same rate as protozoa."

The TDR Program also contributed a disproportionate share to the fields of immunology and schistosomiasis research. In a recent editorial, researcher James Bennett referred readers to an oft-quoted pun: *"'It is not what immunology can do for parasitology but what parasitology can do for immunology'. This is especially applicable to the development of a schistosomiasis vaccine, which has done much to support the field of immunology, but which, in reality, has done little to alleviate the disease"* (Barrett July 2000).

Barrett's point is underscored by an impact analysis conducted in 1986 which found that Foundation-supported schisto investigators accounted for only 3% of the schisto researchers identified in Medline files, yet were responsible for 32% of the total

literature between 1970 and 1984. Within specific literature search categories, this group was responsible for 55% of immunology, and 18 and 9% of the epidemiology and control and biochemistry/drug development literature respectively (Goffman 1985). In total, Program investments resulted in 270 schistosomiasis publications.

Other Schisto Program outcomes included both processes and tangible products. Processes included enhancing information available to field and bench researchers through Foundation publications (most notably *Schisto Update*) and through workshops and meetings. Products included an improved grading system for determining the severity of schisto infection using ultrasonography.

While a schisto vaccine still remains elusive 27 years later, five of the six antigen candidates that have been found to be promising were identified, at least in part, by Foundation-supported researchers. The duration of the Foundation's tenure in the area of schisto vaccine research was a source of much discussion among key informants. One, a self-acknowledged "vaccine skeptic," stated "*Immunology is phenomenology. Ken [Warren] used to say this...The only parasitic vaccine ever was for hookworm in dogs and the vets killed this...Often the answer is good old solid public health, yet vaccination is the holy grail.*"

Other dissenting arguments include the proposition stated in "Antischistosomal vaccines: beyond the laboratory" published in the *Transactions of the Royal Society of Tropical Medicine and Hygiene*, which points to the need for "*a compelling epidemiologic and/or economic justification*" in choosing preventive strategies when alternate interventions (such as antischistosomal drugs) exist (Basch 1993). A highly controversial March 2000 article by Gryseels, "Schistosomiasis vaccines: A devil's advocate view" explores a series of complex epidemiological, methodological and ethical issues. In seeking to "*generate fruitful debate*" before current vaccine candidates undergo human trials, Gryseels contends that vaccines contribute little added benefit, are difficult to assess in terms of safety and efficacy, and may lead to a false sense of security. Gryseels concedes, however, that "*schistosomiasis immunology remains a*

fascinating and relevant subject, even without a vaccine. Considerable long-term investments may not have yielded a practical vaccine, but the spin-offs have made it worthwhile, and no harm has been done-- so far” (Gryseels 2000).

Fruitful debate has indeed ensued. One response to Gryseels’ paper offers the following counter-argument: *“We feel that schistosomiasis cannot be defeated with chemotherapy alone, but rather than arguing the advantages of drugs versus vaccines, we suggest that these approaches are not mutually exclusive, as drugs provide short-term reduction of morbidity, while vaccines hold the promise of long-term prevention”* (Hagan, et al. July 2000). The arguments presented by these scientists, and others, are largely based upon epidemiologic and chemotherapeutic data that have been around for decades or longer, much of which is contained in one form or another in the strategic plans for schistosomiasis research.

Relative to its earliest stated ambitions, the Program successfully contributed to the determination of schistosomiasis’ public health, social and economic effects on its hosts, while spearheading an effort to get these data into the hands of those who could act on it: other international agencies and government officials.

Since the TDR Program’s formation, new schisto control strategies have been developed, refined and implemented, typically using praziquantel, or less commonly, metrifonate and oxamniquine. Although WHO/TDR reports a decline in prevalence (WHO 1995), schisto control remains a significant public health problem, particularly in impoverished areas characterized by poor sanitation and inadequate water supply. Molluscicides and other vector-directed strategies generally proved to be neither effective nor sustainable approaches to control.

Feasibility of control efforts, as identified by one informant, was a significant tension that was difficult to avoid. *“Where we missed the train is having a diagnostic product that is feasible to use, because selective treatment is a better approach than mass treatment.”* The rationale for investing in a diagnostic tool was to improve surveillance

outcomes and targeting. This informant felt that the diagnostic test was not used as much as one would have expected because of the relatively high cost of screening, stating that under conditions where the prevalence of schisto is greater than 25%, it is cheaper to mass treat than to screen. The question remains to be seen whether it would have been worthwhile to invest in bringing the cost of the test down further.

Outcomes also included a number of activities that contributed to helping to build the field. The Foundation stimulated pharmaceutical company research on schisto compounds through direct support when no companies were undertaking this on their own. It established the precedent for patenting Foundation-supported products and development processes to help pave the way for eventual commercial licensing, leading to production and marketing. It established a means to test for product carcinogenicity, a vital part of R&D. It created centralized information resources, critical to helping the field incorporate the latest research results into on-going efforts. And, it fostered the security of a stable funding resource, in addition to NIH, which was considered necessary to attract new investigators into the field.

Alone and in combination, these were important contributions to help build a field from among otherwise disparate and independent research efforts. Nonetheless, these efforts were not systematic enough, or financially secure enough, to continue on their own once Foundation funding was removed. Program staff recognized this, and realized that while they had stimulated the field's growth, they had not put in place the means to perpetuate that growth without a direct influx of funds.

III. The Onchocerciasis Program (\$21.6 million, 1985-1998)

a. Historical Overview of Onchocerciasis

Working on Africa's west coast John O'Neill, a physician in the British Navy, examined microscopically skin from men with "craw craw", a debilitating dermatological condition common in the area. To his dismay, he observed tiny "worms" contorting violently! In 1875, the British medical journal, *Lancet*, published O'Neill's observation's in an article entitled "On the presence of a filaria in 'craw-craw'". These were the microfilariae, or baby worms, released by much larger adult female worms (*Onchocerca volvulus*) living in nodules under the skin.

Microfilariae, found primarily in the skin, also move through tissues to other organs, including the eyes, where they can be found superficially as well as in deep structures of the eye. The death of the tiny microfilariae stimulates the immune system of the human host to react with acute inflammation. The cumulative effect of this, especially in heavily infected individuals, gradually leads to striking changes in the skin and diminished vision or blindness. A French physician in the late 1800s described the disease as one that "*made young men look old, and old men look like lizards.*" Severe itching is characteristic; patients may scratch themselves constantly and some have committed suicide because of the unrelenting character of the itching.

The parasite that infects humans, *Onchocerca volvulus*, is believed to have evolved in African cattle. It is transmitted when Simulium flies (black flies) ingest microfilariae when feeding on the skin of an infected individual. After development of the larval stage of the parasite within the black fly, it becomes infective and is passed on when the insect feeds on another human. Because black flies breed in flowing water habitats (their larvae are attached to the river banks and derive oxygen and nutrition from the flowing water), and they generally are not strong fliers, the disease onchocerciasis is typically distributed on and near the banks of waterways: hence the common name River Blindness. In some areas, especially in West Africa, the impact of the disease has caused

enormous areas of fertile land to be abandoned because it was uninhabitable; half of the adults were blind. An estimated 18 million people are infected, almost all living in Africa. Relatively small foci of onchocerciasis, generally not associated with blindness, are found in parts of Mexico, and in Central and South America.

b. Scientific and Historical Context of the Onchocerciasis Program

Unlike malaria, and later schistosomiasis, onchocerciasis received minimal attention by researchers or public health officials in the post-WWII era. This is largely because onchocerciasis occurs predominately in remote, isolated regions with minimal infrastructure and limited political power. Some 98% of the world's cases occurred in Africa, where most of the blinding disease was found. Lack of safe and effective therapy prevented meaningful intervention; indeed the available drugs typically caused severe side effects. Additionally, the disease was difficult to study outside of endemic countries because inexpensive animal models were lacking, and the long (about one year) life cycle and difficulty in obtaining parasite material for study made it an extremely difficult disease for university-based investigators in developed countries to pursue.

During the 1960s and early 1970s, research was carried out in Kumba, Cameroon on humans and chimpanzees, supported largely by the British Medical Research Council. Epidemiological and clinical studies were carried out in Chad and Zaire. But largely, it was a neglected research area, as indicated by the lack of scientific literature, which trailed that of malaria, schisto and leprosy by at least 3 to 1 (WHO 1980).

The first major control effort was the Onchocerciasis Control Project (OCP), which was launched in 1974 by the World Bank, other donor agencies and developing country governments in seven countries of West Africa. OCP was a massive and ambitious effort to “reclaim” vast uninhabited agricultural regions by using chemicals released from airplanes or helicopters along immense river systems to kill the black fly larvae. OCP has been called by some the “*largest and most successful human disease control program currently being executed*” (Molyneux 1995). Nonetheless, OCP has

faced its share of challenges in maintaining its advances while withdrawing vector control activities. For example, Burkina Faso and four other countries once rid of the black fly later became reinvaded. More importantly perhaps, OCP created new interest in, and recognition of, onchocerciasis and its severe negative impact on the health and economic stability of affected populations.

Oncho was one of six diseases targeted for research and training by the WHO/TDR Program. WHO collaborated actively with the OCP and took responsibility in 1978 for an OCP-supported chemotherapy research unit in Tamale, Ghana. The WHO/TDR Program placed limited priority on immunological studies with the exception of immunodiagnosis. Modest resources were directed at protective immunity or vaccine development. Instead, this program focused primarily to increase knowledge of microfilariae-induced inflammation, antigen isolation, in-vitro maintenance and animal models of onchocerciasis. Because large quantities of biologic materials, particularly infective larvae, would be essential for research leading to vaccine development, recent advances in the ability to produce and preserve live larvae (by freezing) offered modest encouragement. Consequently, an EMCF staff member was advised during a visit to WHO in 1979 that oncho vaccine development would be a good area for the Foundation to consider because it was not targeted by WHO/TDR.

The WHO/TDR Scientific Working Group (SWG) actively encouraged the pharmaceutical industry, including Parke-Davis, Warner-Lambert, Hoechst, Wellcome and others to pursue development of anti-filarial drugs. In 1987 a major treatment breakthrough occurred when Merck decided to donate its microfilaricide Mectizan[®], which made it possible to treat onchocerciasis safely, effectively and with a single dose. Prior to this, two drugs were available and both had severe side effects. Diethyl carbamazine (DEC), could cause severe side effects and sometimes resulted in blindness. The other, suramin, was known to cause kidney failure and death.

The Mectizan[®] Donation Program (MDP) was precipitated by Merck's initial failures in obtaining support from governments, international organizations, or

foundations to support distribution of the drug at low cost in developing countries (Collins 1999). As an alternative, Merck opted to donate the drug through the Task Force for Child Survival. Through the program, Merck has made the drug available indefinitely and free of cost to those who need it for onchocerciasis. The donation program also created a new model for building partnerships for disease control: it brought together private industry and public organizations to focus on a specific objective. While the Foundation deliberated whether to support the MDP, it eventually decided that a vaccine offered the best long-term solution to the problem of oncho control.

c. Onchocerciasis Program Narrative

The Oncho Program developed in circumstances significantly different from that of schisto and trachoma. In contrast to these, the Oncho Program was targeted solely on vaccine development. Although OCP was well underway in Africa and field trials of Mectizan[®] held significant promise for the control of transmission, Dr. Cook contended that neither “*constituted a solution for the long-term.*” Oncho transmission dynamics-- which would require yearly treatment for seven to twelve years to successfully interrupt transmission-- and the enormous cost of insecticidal spraying implicated the need for a vaccine (Cook, et al. 1986).

Based on Foundation-supported workshop proceedings held earlier in the year, TDR Program staff defined an initial aim for the Onchocerciasis Program in April 1985. They sought to determine whether it was possible to define the immune response to *O. volvulus* in experimental animals and to separate protective from deleterious antigen effects within four years. This required the availability of substantial amounts of research material (stocks of infective larvae and cDNA from adult worms), as emphasized by workshop participants. As a result, this component was incorporated later into the strategic plan and several grants were awarded to establish research repositories of parasitic materials. These included a DNA repository of six strains of onchocerciasis from Africa and Central America. The strains were used by investigators seeking to characterize protective antigens that are present in the parasite only in small quantities.

Recombinant DNA technology facilitated production of adequate quantities for testing. To aid in characterizing the immune response in animals, scientists at Johns Hopkins and Cornell produced and distributed third stage *O. volvulus* larvae (L3s), key to this effort. Ultimately, provision of research resources became a significant part of oncho funding, constituting nearly one third of the oncho budget in later years.

By 1986, the Program had four research components aimed at developing an oncho vaccine:

1. Animal Models of Protective Immunity, which supported basic studies that would define the components of the immune response;
2. Immunology and Molecular Biology, which sought to identify, characterize and reproduce protective antigens;
3. Epidemiology and Pathology in Humans, which aimed to increase basic knowledge of pathogenesis as well as variation in human and species responses through assorted geographic studies; and
4. The Vaccine Testing Program, which would test candidate antigens on chimpanzees.

For the next three years, staff reported that scientists were struggling to identify a suitable animal model for oncho infection which would represent a major advance for vaccine testing efforts. Work to develop a large-animal model using chimpanzees and cattle proved elusive, however. A major setback occurred when scientists were unable to induce protective immunity in chimpanzees using live attenuated (weakened) parasites. The chimpanzees developed infection but not the disease. According to one informant, the unique contribution of EMCF to oncho research was that *“by focusing on an area [vaccine development], and supporting needed but not always ‘sexy’ research such as animal model creation [which likely would not have been supported by NIH or other grantors], they could accomplish more than other research funding organizations.”*

Merck's creation of the MDP in 1987 brought two questions to the fore later in that decade: 1) Is there a role for the Oncho Program in evaluating or distributing Mectizan[®]?; and perhaps more significantly, 2) Does the availability of Mectizan[®] *“make the rationale for the vaccine program less compelling?”* For the first time, the Foundation was confronted with a major choice in oncho: support efforts to inform improvements in the distribution and evaluation of an effective control agent in hand, or,

maintain the single course toward development of a long-term prevention measure. After these questions were debated at the April, 1989 Advisory Committee meeting, the group concluded that *“a vaccine to prevent infection still presents the best long-term solution and that the prospects for a vaccine justify our continued investment”* (Cook, et al. 1990). The Program adhered to this rationale as it refined its Program Plans over the next few years, deliberating the specter of Mectizan[®] resistance and the need for a macrofilaricide that potentially could halt transmission more effectively than Mectizan[®].

Although the option of participation in the MDP effort was discussed by advisors and staff, documentation suggests that it was not a serious consideration. Rather, the MDP was apparently viewed as an interim measure and therefore a motivation and rationale for continuing the vaccine efforts. In retrospect, there may have been an opportunity cost for the field by the Foundation not collaborating in either distribution or evaluation of the MDP effort. While the MDP has distributed enormous quantities of drug, few if any formal evaluations have been conducted to assess whether the distribution has been successful in halting transmission, and if not, what operational barriers limit its success. Relative to these questions, advisers to the TDR Program had identified two operational issues previously encountered in the OCP relevant to MDP that may have merited consideration: (1) the effects of lack of coverage for women of child-bearing age; and (2) whether institutional capacity was sufficient to identify pockets of disease. Both of these issues bode a problem for control. Given that the MDP has been a model for several more recent drug donation initiatives, including ITI, exploration of such questions could have informed these and future efforts.

As the earlier programmatic investments in basic vaccine research began to yield returns, staff narrowed its recommendations to four areas representing a tightly focused, but potentially richer opportunity to meet the ultimate goal of an oncho vaccine: (1) antigen identification and production; (2) animal models for screening these; (3) immunological studies in animals; and (4) immunological studies in man. The change reflected the successful development of a small animal model, using infectious (L-3) larvae implanted in diffusion chambers in mice to screen recombinant antigens. This

advance permitted a tighter focus on identifying and screening larger numbers of candidate antigens.

Through 1993, the Program focused on antigen screening activities, recognizing that this “tight rifle shot” approach to vaccine development carried a greater risk of failure than a broader one. The Board recognized this and while some members voiced concern in September 1991 that *“if we focus narrowly and miss, what will we have accomplished?”* the prevailing opinion was to stay the course.

This choice presented a second opportunity cost, also discussed by the staff and Advisory Committee, which was to decide against investing in a macrofilaricide (to kill adult worms) given questions about the sustainability of the current control approaches offered by OCP and MDP. At that time, amocarzine, under development by Ciba-Geigy, looked promising, but failed trials in humans due to toxicity (Ottesen 2000 pers. com.).

Drs. Hoffman and Eric Ottesen, working through the Onchocerciasis Task Force (OTF), reviewed the Program in March 1994 as part of a larger effort to redesign TDR. (Plans were to redirect 25% of the trachoma budget in 1995 when chlamydia immunology research concluded.) Both reviewers found that the Oncho Program had advanced the field forward sufficiently such that its sustainability, competitive edge and continued productivity would be ensured (Cook, Mecaskey 1994). This review signaled the earliest formal designs on an exit strategy for oncho. The next Program Update (June 1994) reflected this shift from development to departure: *“Our role in onchocerciasis will shift gradually to support for program facilitation rather than direct research...we expect that funding would end in 1999, the year in which the Foundation would have completed 15 years of support toward a vaccine for onchocerciasis”* (Cook Mecaskey, 1994).

Following this announcement, the Oncho Program’s scope of work shifted to support of three areas: individual labs developing research resources and/or antigen identification; specific research resources (e.g., DNA library) ; and coordination by the

OTF. In lieu of a final competitive round of grants to individual laboratories, staff proposed to identify “*a single international organization to carry on oncho vaccine development activities into the next century*” (Cook 1996). According to planning documents, this institution would step into the Foundation’s and OTF’s shoes to manage the Oncho Program and utilize its position and financial resources from EMCF to raise additional support from other funders for the vaccine effort. It appears that the plan to identify an organization to carry on the oncho work was infeasible, however, and according to grant records, the staff instead concluded the program with a final round of grants to individual labs. The last oncho grants were made in 1998.

d. Program Operations, Processes and Tools

As in the Schisto Program, staff supported a Vaccine Development Task Force. In contrast to the Schisto Task Force, however, which was established as part of an exit strategy, the Oncho Task Force played a pivotal role in facilitating and coordinating oncho vaccine research and collaboration.

The need for a task force was emphasized by recognition that the worm's successful adaptation had made it a difficult target for vaccine development (only two vaccines had been developed to protect against parasites—sheep lungworm and dog hookworm). A highly coordinated process was needed to separate protective antigens from deleterious ones. This was the rationale for integrating research resources into the formation of the Task Force in 1988, supporting efforts such as collection, storage and distribution of sera from infected and naturally immune people in endemic areas to help characterize the nature of protective immunity. The Task Force coordinated activities of a nucleus of about ten academic research institutions in the U.S. and Europe for more than a decade.

Competitive funding of vaccine researchers and support of private companies were two other tools used in schisto and subsequently in oncho. TDR’s competitive grants program, coordinated by the OTF, began in 1992 with seven grantees (about one-

third of applicants) and ended with support for 14 grantees by the third and final competitive round held at the end of 1995. Two private companies received support, one to produce promising antigens, and the other to evaluate analogues of dog heartworm antigens for their potential use in an onchocerciasis vaccination. This support to for-profit companies was still a rare practice among foundations.

The TDR Program employed a few additional tools to potentiate the effectiveness of the OTF, based on experience with the Schisto Program and on opportunities that arose in this field. One of these was communication. Commensurate with the Oncho Program start-up, the Foundation supported publication of an oncho research bibliography to inform laboratory and field scientists. A 1986 grant supported subsidization of *Parasitology Today* subscriptions to 400 scientists in the developing world. As in schisto, the Foundation published the *Oncho Update*, highly acclaimed by scientists in the field as a major scientific resource. Similarly, the Foundation-supported *Greene Sheet* (developed by and named after the OTF director, Bruce Greene) drew high praise as a valuable clearinghouse for researchers. These communication efforts were developed to serve specific needs of bench and field researchers and were viewed by them as an important contribution. Aware that a more systematic approach to communication was needed in all its programs, the Foundation in 1988 awarded a self-administered grant to disseminate information on the Foundation's programs in general (including oncho) and to provide assistance to grantees.

Policy analysis was another ancillary tool used to further the program. One of three such grants supported a study of the social and economic conditions and consequences of blindness in Mali and Guinea. A second emerged from the debate on whether to support Merck's MDP, and while the Foundation had decided not to play a role, a 1993 grant to the River Blindness Foundation supported an operations research study to assess the long-term impact of Mectizan[®] on oncho in Nigeria and Cameroon. In large measure, according to Dr. Cook, this grant was made in response to requests by other funders to be a “team player.” While the grant supported annual Mectizan[®] treatment in Cameroon from 1993-95 as well as the expenses associated with clinical and

parasitological evaluation of the treatment population, staff viewed this not as a departure from the commitment to avoid direct service delivery, but rather as supporting what advisors considered to be operational research for the MDP (Cook 2000 pers. com.). The third policy grant, awarded in 1997, was intended to mobilize European funding for vaccine research at the time that the Foundation was exiting the field.

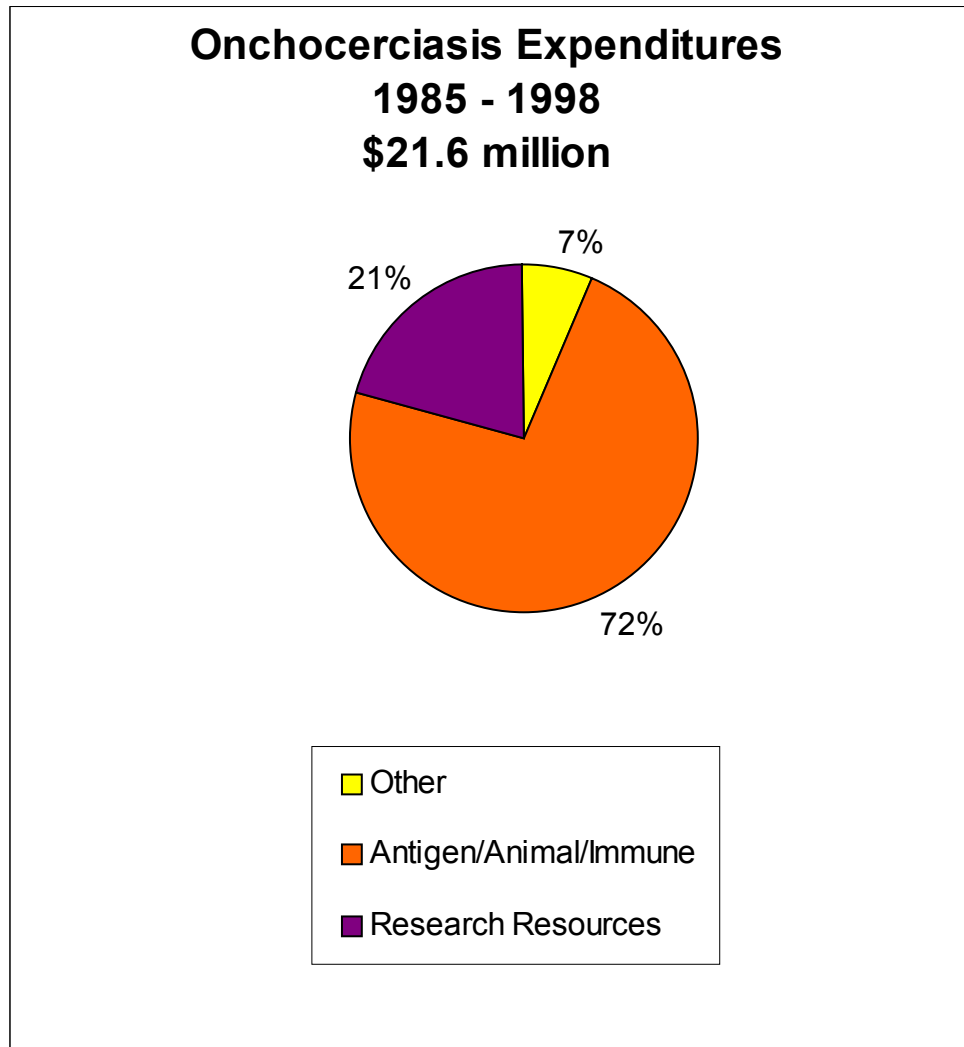
While workshops were an essential tool for information exchange between 1986 and 1991, they became the vehicle to create awareness among grantees of the Foundation's plans to exit the field. This decision was based on results of the formal evaluation of the Oncho Program undertaken in early 1994 by Drs. Hoffman and Ottesen, a former grantee, Advisory Committee member and OTF Director.

As a grantmaking tool, formal evaluation was a rarity. Yet in the case of oncho, it proved valuable by providing the Foundation with an "outside" perspective (although both reviewers had direct involvement in the TDR Program). The evaluation provided vital assessments of approach and progress, successes and limitations, and recommendations based on those. And, it provided an important view for grantees to realize that the changes to come in their direct funding were not capricious and random, but thoughtfully determined. It set the stage for an exit strategy. The assumption behind this exit strategy was that the strength of the Task Force collaboration would position grantees strongly to compete for NIH funding. Although both evaluators made it clear that the development of a vaccine was a long way off, they emphasized that the Oncho Program established and met several goals that moved the field forward to the point where it could effectively *“stand on its own competitively.”*

e. Onchocerciasis Program Outcomes.

Among the Program's achievements, according to Drs. Hoffman and Ottesen, were that it had successfully “assembled materials and reagents for use” in vaccine research, fostered the “understanding of host immune response,” and like the Schisto program, had assembled a cadre of top-notch researchers. In addition to its stipulated

Figure 3. Onchocerciasis Program Expenditures, 1985-1998



goals, the reviewers identified several other achievements—establishing good communication networks among oncho researchers, fostering competition, and correctly targeting bottlenecks. According to Dr. Hoffman’s review, substantial gains were made by 1994, as summarized in the following table.

Table 1: Onchocerciasis Research Resources 1984 vs. 1994 (Hoffman 1994)

RESOURCES	1984	1994
Laboratories	6	30
Antigens	0	50
Larvae	0	100,000/year
Animal Models	1	2
cDNA libraries	0	4

More recently, among some of the more tangible outcomes of the Onchocerciasis Program are:

- **Information and access to materials available to investigators via OnchoNet**
 - A table of 26 characterized *O. volvulus* antigens, with detailed information about the type, source, investigators and references
 - *O. volvulus* antigen database that assists researchers, using a simple search engine, to access current information
 - Available *O. volvulus* cDNA and genomic libraries: listing the currently available six libraries (five different stages of *O. volvulus* and one of *O. ochengi* L-3 stage larvae)
 - Contacts: a list of researchers currently working on onchocerciasis as of April 2000
 - OnchoNet Bookmarks: connections to other filarial and parasite-related web sites
 - The Williams Laboratory: the *O. volvulus* Genome Project based at Smith College

- **Highly successful production and preservation of infective stage (L-3) larvae**
 - Over 50,000 produced for use by researchers
- **Developed and validated two rodent models for antigen screening:**
 - (1) diffusion chamber in mice and (2) *A. vitae* infection of jirds (small rodent)
- **More than 50 antigens identified and characterized**
 - 8 have entered evaluation in the cattle model (using *O. ochengi* homologues) after having been shown to generate protective activity in the diffusion chamber model in mice
- **Serum bank at Swiss Tropical Institute**
- **A rich publication legacy including 86 journal articles and**
 - The Greene Sheets: published from 1992-1995, these newsletters contained a wide range of information about onchocerciasis

Scientists working on vaccine development, especially for relatively large parasites that have a multitude of antigens and potential vaccine targets, generally believe that creation of effective vaccines (and drug targets) are likely to be greatly facilitated by detailed genetic information about the parasite. In this context, the array of scientific resources listed above, including the genomic libraries, are expected to accelerate progress.

Subsequent progress that has been made in the Onchocerciasis Program, reported at the final Foundation-supported Woods Hole Workshop in March 2000, provides considerable encouragement that the vaccine development effort will be sustained in the absence of EMCF financial support. The potential is greater than when the Foundation exited schisto. The exceptionally strong and highly collaborative research network is recognized by many as being unique. *“This group is ahead of many groups at NIAID in terms of sharing knowledge, parasitic materials and reagents. EMCF has helped to catalyze and sustain the research effort; NIH has not provided all the mechanisms needed to sustain such sharing and interactions,”* according to Dr. Michael Gottlieb (Division of Parasitology and Tropical Diseases, NIAID) a participant at the recent Woods Hole workshop. Communications and resource accessibility within this group is

greatly facilitated by the EMCF-supported OnchoNet website that provides, among other resources, a great deal more genomic data than were available for schisto. OnchoNet is also linked to many valuable resources, including the Filaria Genomic Network and a data bank of research materials.

New funding sources and organizational relationships have also emerged. For example, the European Union (EU) has established a new, \$1.5 million/year (for 3 years) onchocerciasis program to support research linkages between EU investigators and developing country partners. Four such linkages have been established. Professor David Taylor, University of Edinburgh, said *“These programs could not have started without the initial Clark support. Clark was the catalyst.”* While EU funds cannot be used for their travel expenses, American investigators will be invited to two scheduled meetings sponsored by the EU, and alternate funding mechanisms exist to facilitate meeting attendance and ongoing collaboration between European and U.S. scientists.

NIAID, through its International Collaboration in Infectious Disease Research (ICIDR) program, recently has created “pathogen specific groups” (PSG), including a filariasis PSG, that will serve as a focus for agent-specific collaboration. Although the funding is modest, it can be used to support meetings, workshops, and visiting scientists from developing countries. The goals of the PSG are to facilitate communication, sponsor small meetings to establish research priorities and “state of the art activities” such as creation of “white papers”, and also provide access to new “opportunity grants” on a competitive basis. Dr. Gottlieb (of NIAID) stated *“NIAID programs, including its International Centers for Tropical Disease Research Network, while not a replacement for EMCF, can contribute importantly to maintaining linkages and productive relationships between members of the oncho/filariasis research community.”* Further, a newly created NIH resource, the Vaccine Special Emphasis Panel, reviews and recommends grant applications for extramural funding for the development of vaccines against infectious diseases. New genome-sequencing resources at NIH also may facilitate oncho work in the future. One key member of the oncho research community

has an NIAID grant to create a “consortium” to pursue a major funding effort targeting foundations and other potential grantors.

Finally, important research “breakthroughs” have opened an exciting new range of avenues for research to control onchocerciasis and other filarids. Scientists have found that a rickettsial organism, *Wolbachia*, lives symbiotically within probably all filarids, including *O. volvulus*. This organism is crucial to the development, viability and fertility of filarial parasites. Currently there is an explosion of promising and highly fundable research planning related to *Wolbachia*, much of which involves sophisticated molecular and genetic approaches in seeking new targets for attack.

Although the Foundation did not directly support the *wolbachia* work, the discovery very likely would not have occurred if it were not for the oncho research network it created. According to one scientist, informal exchange within this group helped lead to the “breakthrough.” Another investigator indicated that as a group, the oncho genomic scientists might approach a major private funder to support genetic mapping of *wolbachia* from *O. volvulus*. According to this researcher, having the full genome may identify targets for vaccines, and *wolbachia* might be used as a vector to move genes, an area of research likely to receive high priority.

While the impact of *Wolbachia* research on oncho control remains to be determined, the first effort to use the new knowledge to successfully treat onchocerciasis in humans was published in the April 8, 2000 issue of the *Lancet* by a German investigator previously supported by EMCF, Dr. Achim Hoerauf. Professor David Taylor, Univ. of Edinburgh, observed “*were it not for EMCF’s investment in onchocerciasis research, O. volvulus would have become an “orphan parasite.”*”

IV. The Trachoma Program

a. Historical Overview of Trachoma

Trachoma is the leading cause of preventable blindness in the world today. It is a chronic, progressive disease acquired early in childhood, but with serious manifestations appearing later in life. Chronic eye infection by *C. trachomatis* produces inflammation which progresses to scarring of the conjunctiva and the growth of a membrane with blood vessels over the cornea. The conjunctival scars cause deformity of the eyelids so that the eyelashes turn in and rub against the cornea. This constant abrasion leads to corneal ulceration, often with infection by other destructive bacteria that worsen the degree of corneal scarring and loss of vision.

While the precise means of transmission of *C. trachomatis* are not fully understood, it is clear that the disease is closely associated with rural poverty, inadequate disposal of human and animal waste, poor personal hygiene, arid environments and limited access to water. In some regions, eye-seeking flies that feed on ocular discharges appear to play an important role in transmission. Direct transmission from eye to eye occurs when ocular discharges are spread by fingers and shared towels. Although partial immunity occurs with infection, children and adults are often re-infected. Young children are disproportionately infected and serve as the main reservoir of the organism. Typical late complications, such as in-turned lids and vision loss, increase progressively in older people although they no longer have active infection.

The disease has been well known since antiquity and in the 19th century was still widespread in Europe. In the early 1900s the disease was recognized as a major cause of blindness in Eastern Europe, the Mediterranean countries, Middle East, India and China. Blinding trachoma was also common in the U.S. among the European- descended population of Appalachia and the mid-South, and in Native Americans of the plains and Southwest.

First identified in 1907, and isolated in 1957, the causative agent of trachoma belongs to a group of organisms known as *Chlamydiae*. Initially believed to be viruses because of their small size and their need to grow within living cells, they are now classified as bacteria. One species (*C. trachomatis*) causes a range of human diseases. Specific subtypes (serovars A, B and C) cause trachoma. Other serovars (D through K) are sexually transmitted strains that cause tubal infertility in adult women and pneumonia in newborns; lymphogranuloma venereum strains (serovars L1, L2 and L3) are also sexually transmitted but cause extensive disease of the genital tract and the immune system. A second human species (*C. pneumoniae*) causes pneumonia and heart disease in adults. A third species (*C. psittaci*) infects birds and other vertebrates but occasionally causes human pneumonia and abortion.

Disease severity and prevalence decline dramatically and disappear as economic conditions improve. However, blinding trachoma continues to be a major public health problem among the most impoverished inhabitants of developing countries in much of the world including Africa (both north and sub-Saharan), parts of the Middle East and Indian subcontinent, South-East Asia, certain regions of China, and among Australian aborigines. Currently, 600 million persons are at risk of acquiring trachoma, 150 million are infected, 11 million have in-turned eyelids requiring surgery and 6 million are blind from it.

b. Scientific and Historical Context of the Trachoma Program

Despite its recognition since antiquity, trachoma attracted minimal attention from the research community. With the disease impact mostly in remote, impoverished regions, and seemingly insurmountable obstacles to its control, blinding trachoma was largely ignored except for a handful of investigators and public health workers. Maintenance of chlamydiae in animals and tissue culture for research purposes was done in only a few specialized laboratories. By the 1920s, a number of control programs were established in Egypt and North African and other countries, using a system of base and mobile hospitals and clinics.

The WHO was a strong, early supporter of trachoma control and treatment programs. Its trachoma program, initially based in Copenhagen, moved to WHO, Geneva about 1958 as the Trachoma Program in the Division of Bacterial Diseases. Control projects were carried out in a number of African and Mediterranean countries. Additionally, Trachoma Expert Committees met periodically.

A major breakthrough in trachoma treatment occurred in 1937 with the demonstration that the antimicrobial, sulfanilamide, was highly effective in curing inflammatory trachoma in children and adults. Treatment programs using this drug carried out by the U.S. Indian Health Service during 1938 to 1942 eliminated trachoma in many tribes. When active trachoma was found again in 1956 in tribes in New Mexico and Arizona, antibiotic-based control programs among Indians were started again in 1960, and achieved elimination by the mid-1970s. This provided an important lesson, however, that control and elimination of trachoma can be an on-going, cyclical process.

Because allergic reactions to oral sulfa drugs were relatively common, however, most WHO-associated community-wide treatment programs changed to topical tetracycline, even though topical treatment required longer periods of use and was less effective. Treatment programs in the Mediterranean and elsewhere were assisted by the WHO and by governmental and non-governmental organizations, but in general they were assigned low priority and enjoyed limited success and sustainability. The use of tetracycline was considered less than optimal by one informant: *“Tetracycline was just hopeless, sticky, painful...there are probably little kids that still run away when they see a white man coming...it was just torture for the kids.”* Some national programs included health education and offered limited surgical services to prevent in-turned eyelashes from causing corneal trauma, secondary bacterial infection, and blindness.

A second major breakthrough occurred in the 1990s when a single oral dose of Pfizer's Zithromax[®] (azithromycin, an erythromycin derivative) was shown to be an effective and safe treatment for active trachoma. This antibiotic became the recommended treatment for genital chlamydial infections in the late 1980s, and by the

early 1990s Zithromax[®] treatment trials for trachoma were carried out in the Gambia, Egypt, and Saudi Arabia. A subsequent trial of community-wide treatment (the “ACT trial”) in three African countries, funded in part by the Clark Foundation, confirmed the high therapeutic effectiveness of this antibiotic in treating blinding trachoma.

Other important advances include the development of DNA amplification diagnostic tests for genital *C. trachomatis* infection which are now available, and which have a high degree of accuracy. These tests provide a valuable tool for diagnosis of individuals’ infection, and for monitoring the impact of control programs.

Between 1961 and 1998, at least nine major research meetings on trachoma and chlamydial infections took place in North America and in Europe. With the recognition in the 1970s that *C. trachomatis* was a major cause of sexually transmitted disease (STD), the emphasis in these meetings and most chlamydial laboratories shifted from trachoma to STDs. Nonetheless, several other chlamydial laboratories are currently involved in trachoma research including two American, two British, and *L’Institut d’Ophtalmologie Tropicale de l’Afrique* (IOTA) in Mali. These laboratories collaborate actively with investigators in trachoma-endemic regions of the world.

The WHO effort, now called “Programme for Blindness and Deafness,” has been directed since 1981 by Dr. Bjorn Thylefors. Various WHO documents were developed to assist national programs including three funded by the Clark Foundation. Early vaccine trials begun in the 1960s ended in the 1970s when they failed to demonstrate success in curing or preventing trachoma. These efforts, which ended about the time the Foundation's TDR Program began, were carried out by several academic centers and their developing country partners with funding from the NIH, and other public and corporate funding sources. With the recent (1998) publication of the complete genome of *C. trachomatis*, however, new vaccine candidate proteins now have been identified.

c. Program Narrative

Following the Board's decision to withdraw gradually from schistosomiasis research, staff initiated the design phase for the new trachoma program in early 1984, a year in which neither the NIH nor WHO made any grants to support research on blinding trachoma (Cook, et al. 1986). Based on their reputation in the schisto field, the Foundation's presence was welcomed: *"Clark took on orphan diseases when no one else would. NIH didn't give a [hoot] about trachoma...there was very little funding outside of Clark for trachoma ...without them, there would've been nothing."* As another informant pointed out, *"Funding was drying up. Clark rescued the field."*

The Foundation's approach to trachoma appears to have been heavily guided by the staff's experience in developing the Schistosomiasis Program. Similar strategies were employed, such as early co-option of leading scientists and workshops to develop a scientific agenda and encourage networking between bench and field researchers.

A Foundation-sponsored workshop organized by the International Center for Epidemiologic and Preventive Ophthalmology was convened at Coolfront, West Virginia in 1984 to consider and establish research priorities for trachoma control. Leading investigators reviewed the state of knowledge about the disease and its causative organism, providing an invaluable starting point for developing the strategic plan for trachoma research. Control rather than elimination of trachoma was targeted as the goal because elimination was considered unlikely, given the virtually intractable living conditions associated with the most vulnerable populations.

The 1985 strategic plan for trachoma focused on two major areas, (1) Pathogenesis and Immunology and (2) Epidemiology and Control. Because the pathogenesis of trachoma involved immunologic mechanisms, a potential vaccine could aggravate as well as protect against disease. Thus, much of the early research (in animal models) focused on the mechanisms by which trachoma caused eye disease. This was an effort to separate protective antigens from potentially damaging ones. From an

epidemiological perspective, emphasis was placed on identification of specific risk factors for disease, such as facial hygiene. The relative advantage of systemic (orally administered) versus topical antibiotics in preventing blindness at the community level was explored. Recognizing the critical importance of community participation, cultural and behavioral research needs were also included in the plan.

Unlike the initial outline of goals and objectives for schisto or oncho, both the pathogenesis/immunology and epidemiology/control areas in trachoma were accompanied by a rationale and timetable for completion that would signal subsequent steps. Potential bottlenecks were identified at the outset and the program strategy became a series of logical steps to reach the two goals. For example, staff recognized that accurate field diagnostic techniques were essential to epidemiological surveys and ultimately program design and evaluation. Thus, an early, significant investment for the program was to develop a simplified system to diagnose clinically and grade signs of trachoma for use by paramedical field staff.

By 1988, WHO was ready to implement the grading system in a 12-country training program, and data from Clark-supported epidemiological studies of risk factors had identified poor facial hygiene as a significant risk factor for trachoma infection. At this juncture, staff decided to test this hypothesis through support of a community intervention trial of face-washing in Tanzania.

Staff recommended and received approval from the Board in 1990 to refine and narrow the research questions addressed by the Immunology and Vaccine Development subprogram, citing “budgetary restraint” as a factor. In contrast, staff recommended expanding the Epidemiology and Control subprogram that had yielded important data in several diverse areas relevant to control efforts. For instance, although not cited in the original strategic plan, the value of tarsal rotation surgery in preventing blindness from trichiasis and the feasibility of having nursing staff perform the procedure were established through Foundation grants. The grading system, important to screening and surveillance efforts, was distributed as teaching materials in 12 endemic countries. Field

trials verifying that trachoma transmission could be controlled and sustained by face-washing suggested a role in developing and disseminating a plan for community control.

TDR sought to work with UNICEF and WHO on demonstrations that might include community mobilization, hygiene and water use, treatment and prevention, through existing primary health systems. In addition to the program's accomplishments, an unanticipated factor in control—the promise of Pfizer's (oral) Zithromax[®] to replace tetracycline antibiotic ointment—also became apparent.

Progress in the Immunology subprogram was incremental by comparison, and staff reported that *“unless a trachoma candidate vaccine for human trials is forthcoming, research on immunology and vaccine development will merge with existing efforts on the increasing problem of chlamydial infections of the genital tract and lungs. We therefore expect trachoma work to end in 1995”* (Cook 1991). Dr. Cook stated that although the NIH was already quite active in chlamydial research, funding might increase given the increasing prominence of STD research adjunct to HIV investigations: *“When chlamydia was identified as risk factor for HIV it took off. Our contributions were not as important—we had a deliberate exit strategy based on NIH's presence.”* Thus Dr. Cook anticipated that increases in the NIH budget for chlamydia would “soften the blow” when Clark eventually began to decrease funding for this subprogram (Cook 1992).

After initial evidence suggested that Pfizer's long-acting single-dose antibiotic Zithromax[®] might be effective in treating trachoma, the Foundation hosted a meeting with NIAID, the National Eye Institute and Pfizer to develop plans for assessing prospects for the drug's use in trachoma control. As stated in the November 1992 Program Update *“We have initiated discussions on how Pfizer might contribute to trachoma control in a manner similar to Merck's participation in oncho control. The market is already ripe in the industrialized world, we hope to capture Pfizer's interest and good will and humanitarian benefit through careful use of the drug in trachoma control.”*

Within three months, planning for an NIAID-funded multi-center community trial of Zithromax[®] had commenced. Plans were to test the drug through clinical trials in Tanzania, Egypt and Gambia, coordinated by Helen Keller International (HKI) a major non-governmental organization (NGO) whose mission centers on vision and eye health. In addition to assessing the efficacy of Zithromax[®] in a field setting, the group sought to attain WHO's imprimatur for the use of Zithromax[®] as part of the SAFE strategy. In WHO's GET 2020 (Global Elimination of Trachoma by the year 2020) Alliance, the original plan had been to use tetracycline for the antibiotic component⁶.

In an exceptional public-private collaboration orchestrated by the Foundation, Pfizer and NIAID supported the Zithromax[®] trial while the Foundation assisted research teams in these countries to develop a standard protocol. Abbott Laboratories provided the test necessary to identify the chlamydia antigen.

At this time, staff recognized that funding for control efforts might require extension beyond the 1995 deadline and suggested a number of drug-related avenues of investigation to explore within a broader operations research model. These included impact studies, cost-effectiveness analyses, data collection, surveillance and monitoring.

In 1994, staff presented the Advisory Committee with what they referred to as the "dilemma" of trachoma's "future orientation." Staff's attention had turned "*to promoting and facilitating the integration of trachoma control into national primary care systems.*" The establishment of regional resource and training centers to further promote the strategy seemed a likely vehicle. The pros and cons of linking these centers to WHO was presented to the Board and advisors. Staff made the case that an independent institution, though lacking the WHO imprimatur and dependent upon Clark funding, would be less burdened by the bureaucratic and political considerations incumbent upon a WHO collaboration. This was based on the assumption that the centers could "*enhance the*

⁶ Countries that participate in the WHO GET2020 alliance to eliminate blinding trachoma, that have not been selected to work with ITI, typically continue to use tetracycline ointment.

capacity of countries to undertake their own [trachoma control] efforts” (Mecaskey and Moise 1994).

Thus began the program’s exit from the Epidemiology and Control subprogram, by shifting the balance of responsibility for action to the countries themselves through a determined focus on capacity-building and continuing efforts to raise awareness of trachoma among funders. *“If we do manage to raise trachoma’s profile by 1998, we would expect other agencies to join in support of control efforts. We will wind down support with a terminal set of matching grants”* (Cook and Mecaskey 1994). In June 1994, the Board approved a plan to facilitate trachoma control through primary care systems via support of training and operations research.

Just over a year later, in September of 1995, Dr. Cook reported that Pfizer had expressed interest in a donation program along the lines of Merck’s MDP. Morocco, which had recently set the year 2000 as a target date for the elimination of trachoma, became the candidate for the trial donation effort.

In December 1996, staff presented a five-year, four-part plan for concluding the Trachoma Program. The plan’s primary objectives were to advance the SAFE strategy, support its replication, and advance WHO’s GET2020 goal utilizing the SAFE strategy by working in select countries. Additional objectives were to increase investments by mobilizing and coordinating other technical and financial resources for trachoma control efforts, and to *“develop an institutional locus for advancing the GET2020 goal.”* Each aspect of this strategy implied a deliberate effort at crafting a responsible departure that would perpetuate the SAFE strategy by ensuring that SAFE would be accessible, replicable and sufficiently endowed. In this way, the TDR Program systematically attempted to create a sustainable future for its efforts.

Through continued collaboration with Pfizer, it became evident that the Program’s role in securing the future of SAFE was unique: *“Our challenge is to continue to ‘smooth the road’ so that Pfizer remains comfortable with its philanthropic*

investments in trachoma, satisfied with the results, and therefore willing to increase its commitment to the elimination of disease.”

The need for an institution to continue the highly intensive work of the Trachoma Program also became increasingly evident, as did Pfizer’s preference for an independent, rather than WHO-based, institution. Eighteen months into the five-year exit strategy, Pfizer committed to moving forward in four to six countries, through the Trachoma Task Force. Through discussions with staff and Pfizer representatives, the Board and Pfizer decided to establish the International Trachoma Initiative (ITI) as a 501c3 organization with Dr. Cook and TDR Program Officer Jeffrey Mecaskey at the helm and designated ITI Board members from Clark and Pfizer. These plans were announced in February 1998 and reported widely.

As one member of the Clark Foundation and ITI Boards recently commented, *"When ITI first surfaced, I was one of its strongest proponents. It was a fantastic way to improve our efforts. The Foundation likes to leverage other resources. So, we try to pick our shots very carefully. When the idea of working with Pfizer came up...we realized it would combine Pfizer's resources with the expertise of Joe and Jeff [Mecaskey] in dealing with ministries of health in Africa. It seemed to be a fantastic opportunity. Pfizer is a world class pharmaceutical company... I hope it will be a forerunner of other Foundation efforts, and other foundations' efforts too, not just Clark. That's the measure that we'll be able to lay out."* This reflected sentiments of another Clark/ITI Board member as well, who said *"It was fortuitous and timely. I wouldn't have planned it this way, but once Pfizer decided to donate Zithromax®, it was a “no-brainer.” I'm not sure where trachoma would have gone if this hadn't come about, but the opportunity arose in part because Joe had his thumb on the entire field. It was logical and fortuitous because Joe made it so.”*

d. Trachoma Program Operations, Processes and Tools

The TDR staff employed many of the tools used in the schisto and onchocerciasis programs, but tailored them to facilitate implementation of the several products that became available during the life of the Program. Because Epidemiology and Control was such a significant aspect of the overall strategy, staff adapted them to reflect this emphasis, for example using communication measures to inform and train health workers. With implementation of the Program's exit strategy, emphasis moved increasingly toward a focus on control and ultimately toward building an institution (the ITI) to catalyze and facilitate trachoma treatment in targeted developing countries.

The Task Force mechanism was invoked in 1987 to coordinate and oversee trachoma vaccine development through immunology and antigen studies, animal model studies, and research resources (although this latter area was much less pivotal than in the Oncho program). A 1990 competitive grants program produced 11 vaccine-related research projects, whose scientific direction had been greatly informed by a workshop held the year before. Among the critical next steps identified by workshop participants were the need to work out the structure of a particular surface antigen, other possible antigens, and to determine what role mucosal immunity plays in chlamydia infection. This direct interaction between workshops and grant-making directions persisted throughout the program.

Largely because the vaccine-related work failed to generate early success, while simultaneous efforts in epidemiology and control became highly promising, the Trachoma Task Force was shifted to Helen Keller International (HKI) in late 1992. As noted to the Board by staff, *"Recent developments in the field point to a need for the Trachoma Task Force to make a transition...[This] will allow staff to take advantage of HKI's extensive field network in trachoma-endemic Africa and its working relationship with the WHO Programme on the Prevention of Blindness."*

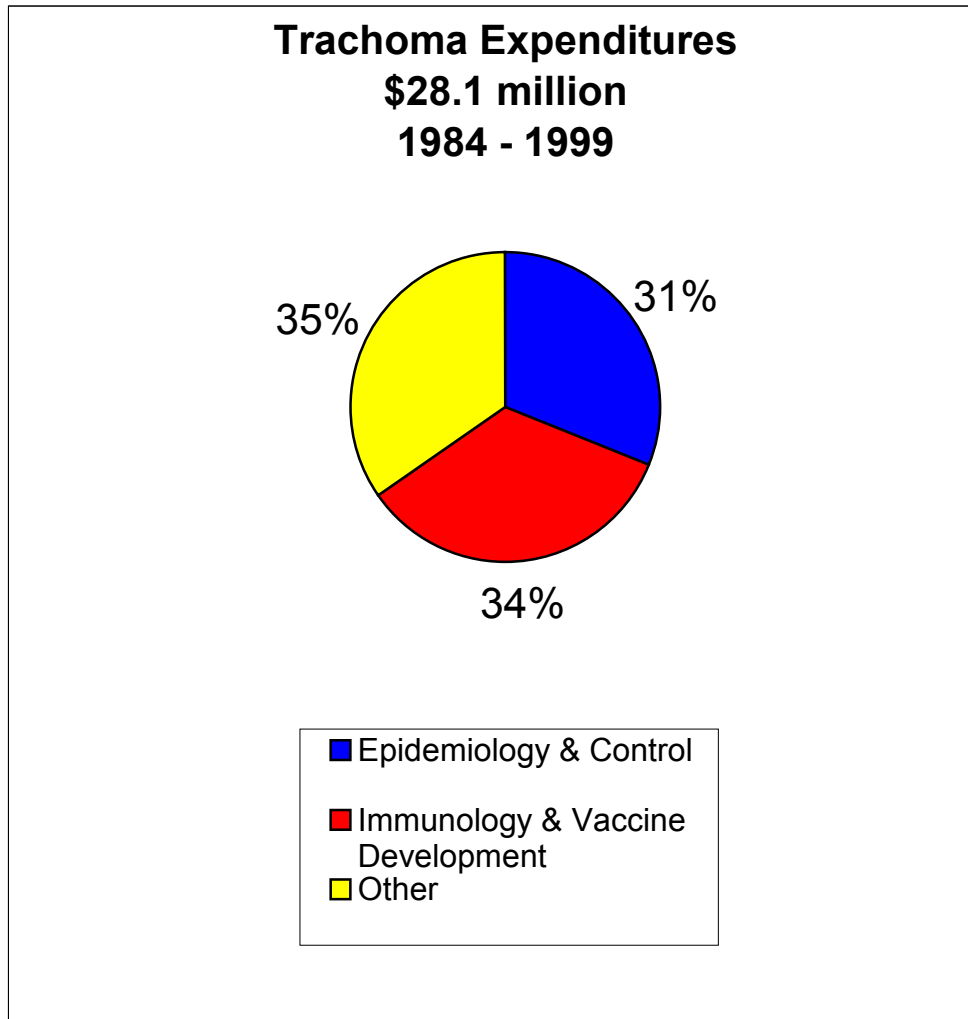
Some in the field, however, were not as comfortable with the selection of HKI or Clark's lack of transparency in making the decision: *"A lot of people thought WHO should have played secretariat, rather than HKI. The process was not transparent— the end run around WHO seemed odd to a lot of people."* According to recent comments by Dr. Cook, a pivotal factor in selecting HKI was the organization's flexibility, along with continuity provided by a key Task Force director who was moving from Hopkins to HKI. *"We stumble, though,"* Dr. Cook said, *"when we don't keep the field informed. In retrospect, we needed to bring people into the process of decision-making. But, there is always a balance between keeping lines of communication open and making decisions. People think the only strings foundations have are those that tie the money bag."*

The striking advances in control from grant-supported demonstrations of the efficacy of face-washing, surgery to correct trichiasis, and the simplified trachoma grading system, were enhanced by related health education of communities and training of health workers. HKI, with its expertise, network, and flexibility was seen as the best opportunity to help countries implement these control techniques.

Another addition to the Program's toolbox was the highly developed communication strategy that spanned information to the scientific community, health care workers, and people in poor communities afflicted by blinding trachoma. Not only were materials produced, as in the other two programs, but funds also supported training of nurses in the surgical technique, health care workers using diagnostic tools, and those undertaking health education efforts. The communication efforts with trachoma were strategically designed to include training for some of the field projects.

The Program also used its convening function to facilitate the early, essential discussions between the NIAID, the National Eye Institute and Pfizer in 1992 on clinical trials of Zithromax[®], essentially brokering a critical public-private partnership that paved the way for Pfizer's subsequent drug donation program. By supporting HKI to coordinate the multi-center trial to assess Zithromax[®]'s efficacy (which staff considered necessary to receive WHO's endorsement of its use), the Foundation played a pivotal role. Fully 22

Figure 4: Trachoma Program Expenditures, 1984-1999



grants made between 1996 and 1999 supported further assessment of the drug, its implementation, and assessment of its effectiveness as part of the SAFE strategy. This highly structured and purposeful strategy proved an effective and efficient march toward creating the conditions necessary for the prevention of blinding trachoma in the future.

e. Trachoma Program Outcomes

Of the three disease research programs, the products of the trachoma prevention effort have received the most prominence by virtue of their immediate and widespread application. Development and dissemination of several key products, and the means to implement them on a broad scale, have created a systematic approach for controlling trachoma and helping to prepare the field to perpetuate its continued control in targeted countries. The trachoma grading system, one of the earliest programmatic efforts, has been employed by WHO in multiple countries, improving the accuracy of epidemiologic surveys as intended, and serving as a training tool for community health workers. Development and refinement of the SAFE strategy has also contributed enormously to the body of knowledge surrounding low tech, sustainable preventative measures protective against blinding trachoma. Evaluation of a surgical field technique has averted untold cases of blindness from trichiasis. The establishment of Regional Resource Centers in Africa, as well as numerous other resources such as WHO technical manuals and a four-part CD-ROM tutorial on blinding trachoma for health workers, have all helped to develop in-country capacity for trachoma control.

With the Foundation's support, trachoma immunology research also was advanced during the life of the program. Chlamydial proteins that could generate an immune response were identified, and the gene for one of these proteins, the major outer membrane protein (MOMP) was cloned and its immunologic structure mapped. The portions of the molecule responsible for immunity conferred through antibodies and certain white blood cells were identified, a significant advance towards selecting appropriate antigens for animal trials. While progress was achieved in developing a

small animal (mouse) model, the continuing absence of a suitable model continues to hamper vaccine development against blinding trachoma.

Foundation-supported research also contributed important knowledge about the role of mucosal immunity in preventing or clearing infection, and the contribution of cell-mediated immunity in clearing infection and in the development of blinding trachoma. In total, 122 peer-reviewed journal publications contributed to the fields of trachoma immunology and epidemiology.

Telephone queries to several individuals knowledgeable about preventable blindness in developing countries, many of whom are affiliated with international eye NGOs, indicated that the Foundation's efforts have "*unequivocally increased awareness of,*" and concern about, trachoma relative to the other common causes of preventable blindness. While acknowledging the difficulty in quantifying impact, one informant said "*I believe that Clark's commitment to trachoma has prevented a lot of blindness, and certainly it has raised trachoma on the radar screen.*" Another expressed the view that trachoma is more global in distribution than onchocerciasis and Vitamin A deficiency and, as such, merits more attention. Consequently, the ITI has provided a new and needed force in the community of "blindness" NGOs.

f. Advancing Outcomes Further: The ITI

The ITI is the critical vehicle established to sustain the progress of the trachoma outcomes generated by the TDR Program. It has both remarkable opportunities and daunting challenges, and it will be vital to the Foundation to have evaluators in the future assess the extent to which ITI has fared and helped to advance the field. This will require anticipating likely problems and means to address them.

One of these challenges is attaining self-sufficiency. As currently designed, the ITI is expected to secure future funding from other sources. By virtue of its independent status as an intermediary organization, it can be viewed as a stand-alone organization that

potential funders might be interested in supporting whereas they might be less likely to do so if ITI were a Clark Foundation subsidiary. There are ample precedents for this, such as the Corporation for Supportive Housing model that has been described to the Board by President Michael Bailin.

Additionally, if Pfizer is planning a long-term commitment for Zithromax[®] donation that is similar to Merck's commitment for the MDP, the presence of a long-term private sector funder may be a strong magnet for attracting other foundations' funds. Successful outcomes from the initial five countries also would be likely to strengthen funding prospects. WHO's imprimatur may be an additional incentive for international donors to participate. At this writing, the Foundation is awaiting creation of a fully developed business plan from ITI.

Reflecting on the financing issues, one joint Clark/ITI Board member said, "*ITI is eventually to become self-sustaining. That's an important matter of interest to both Clark and Pfizer. If we achieve success, there should be contributions coming in from others, like the U.N. We'll be keeping a look out on where support may come from. We welcome contributions now. They either need to be consistent with our goals, or if the goal is broadened by others' involvement, we have to make sure their contributions are sufficient to achieve that expanded goal. We'll cross that bridge when we come to it. I hope the ITI will stand at the forefront and attract other funding over time.*"

Another potential challenge is maintaining the conditions necessary to preserve the partnership with Pfizer. The ITI is highly dependent on continued drug donation by Pfizer. Yet several factors currently recognized, and others not yet known, may influence Pfizer's continued commitment. For instance, Pfizer will lose its international patent in April 2001, and its U.S. patent is scheduled to expire in 2005. Both situations open the way for manufacture and sale of inexpensive generic versions of Zithromax[®]. This is anticipated to decrease revenues substantially from all uses of this highly profitable drug. In turn, this may diminish Pfizer's resources for continuing to donate large amounts of the drug. As a Clark/ITI Board member recently discussed, "*Patent limits are a challenge.*"

...It might bring price down and bring in other sources of inexpensive drug. But what we're setting up is a model that can be used as a template for other programs. It's a moving target going forward. It may look different 10 years from now. It's flexible and we're learning as we go along that we'll have to be responsive, watch after our investments."

Other factors that may influence Pfizer are the multiple obstacles being faced by several companies that have been or recently began donating drugs. These include problems with distribution, customs taxes, expired drugs, market "leakage" (diversion), and in one case, liability claims. Are companies likely in the future to begin to look for other incentives such as tax breaks on U.S. sales revenue, or longer patent protection to offset these disincentives? These issues, if they arise for the ITI partnership, may lead to creative new approaches rather than breaking the joint effort apart. Insight from a joint Clark/ITI Board member addresses this. *"There are hazards, challenges too. It's true that most joint ventures don't work well over time. The parties' interests begin to diverge, and partners split up over time, at least that's the classic business experience. But we've built protections to protect Pfizer and to protect Clark. Both have to agree on major decisions. So far, it is working beautifully, and I remain enthusiastic..."*

"One reason why this may be different from a classic business example (of broken joint ventures) is that we're not in this to make a profit. While sometimes (in business ventures) a clash of egos causes the split, usually it is economic issues that cause parties to diverge. While Pfizer has its own business interests, and these may in the future lead them to select certain countries to work in, or we might prefer some countries that Pfizer does not want to work in, our joint goal is preventing blindness from trachoma."

Pharmaceutical companies are taking a beating in the press over high U.S. drug costs and lack of attention to diseases afflicting people in developing countries. Such press can either stimulate a greater commitment by companies to enter into and maintain donation programs, or it can discourage them from entering because of the bad press that will ensue if they decide to leave or if their efforts are dismissed as miniscule relative to

the need. Communication strategies, a challenge and opportunity, will be essential. As one informant commented, "*[foundations] rely too much on news (print media) conveying information but not persuading and connecting. It's through the latter that communication can help in field- and institution-building.*"

Another challenge for ITI in strengthening the field's capacity to decrease blinding trachoma will be navigating the complex relationships among the various ITI stakeholders, multinational organizations, in-country governments and NGOs, other potential funders, and potentially other private sector partners. Creating the conditions for all of them to continue to share the same essential goals, and to be willing to sustain their commitments over time, may require intermittent development of incentives and removal of obstacles. There are many unresolved issues that these stakeholders will have to tackle. For instance, ITI, a member of WHO's GET2020 alliance, has been criticized by WHO for its unilateral selection of the five ITI demonstration countries. ITI will be challenged to strike a balance between meeting its institutional needs and fulfilling its obligations as a member of the alliance.

Additionally, according to one informant, ITI faces the "black hole" phenomenon that is intrinsic in vertical (single disease) programs. When treatment and prevention are successful, prevalence drops, and field monitoring then becomes less vigilant. This leads to a resurgence of disease, as occurred with trachoma control efforts among Native Americans noted earlier. This requires sustained political will in targeted countries to continue to monitor and address trachoma control.

It will be important for ITI to identify early on these and other issues that arise and to think imaginatively about how best to create conditions to sustain progress. An evaluation of ITI's role in advancing the field will need to capture these. Two joint members of the Clark/ITI Boards provided a sense of what information will be important. "*Can we work effectively in the countries we're working in? There is corruption... squabbles about who gets what resources when the test is over. It's difficult to be sure the money is well directed. I believe Joe and Jeff have figured out ways to do this...Are*

countries putting their own money into the project? When you go away, will the effort disappear? Those will be outcome measures I would like to see as part of the progress toward a self-sustaining effort. We will begin to break the cycle of infection, but the efforts will have to be maintained or blindness from trachoma will reappear. If we are able to document savings and the contribution of blindness averted, we will justify having politicians in these countries put some money in the budget for sustaining the program. We need to be sure the credit is shared with others, including the politicians, so that they will want to be seen as part of this effort."

"ITI is going to have to come up with data to show this is working, that it's making an impact in saving sight. Then we could be a model for others to contribute to, or to emulate. Other foundations should want this type of data to see if it works. Part of the SAFE strategy is environment, and other foundations may want to work on this...It could be very beneficial in addressing an important part along with the other three."

"...This effort needs a champion. In Joe, we have that. He is universally admired as a terrific international practitioner. That is very important. Of course, it's also a real issue, because it makes ITI very person-dependent. Let's hope we don't have to worry about that for a long time."

The ITI and the Foundation are poised to make a fundamental contribution to strengthening the trachoma control field, and to strengthening the field-building field. It is a wonderful opportunity. As one Board member commented, *"With ITI, we have seized the moment, and have developed a partnership that is carrying progress forward through this intermediary. It is elegant. We don't care who gets the credit, it's creative and the best form of modesty."*

V. The Independent Commission for Health Research and Development

Clark's leadership role was typified by a series of grants in the mid-1980s that gave rise to the Essential National Health Research (ENHR) movement. Dr. Cook requested funding for a new budget category—a “*small venture into other efforts*”—during FYs 86-88. Three opportunities were proposed, including a revolving fund for health technology, a research leadership initiative, and an international health research group modeled after the Consultative Group for International Agricultural Research (CGIAR).

Staff sought to frame the salient issues of health and development within a broader, integrated context for international health (IH) funders involved in or interested in research efforts; after consideration of various alternatives, staff pursued the CGIAR model as most proximal to its interests. Dr. Cook reasoned that there was a compelling need within the field to examine formally the opportunities and barriers for research in the developing world, and that these data could help guide future efforts by other IH funders. Embedded in this exploration was the need to wrestle with the controversy of whether to build in-country research or perpetuate the assumption that the field would progress faster through investment in the research resources of developed countries.

A commissioned strategic planning document identified the “*serious health need*” and “*misallocation of existing resources*” in the developing world. Although research and development were recognized to be a “key factor” in improving health in lesser developed countries, only a fraction of potential resources had been mobilized: “*The health community is not doing an adequate job in presenting the case for research and development to either the funding agencies or the scientific community*” (IDAU 1985). Staff concluded that a close examination of the organization, funding and execution of research and development activities for health was needed: “*Whatever mechanism emerges should also serve as forum so that interested donors can have access to authoritative assessment and identification of opportunities...an annual review will*

provide advocacy function, enhancing participation in the field and strengthening existing programs” (IDAU 1985).

Given the collaboration required for such a broad endeavor, staff recognized that the proposed study must have cooperation of, but *independence* from, multilateral organizations such as the United Nations Development Programme (UNDP), The World Bank, and WHO. Thus in 1987, the Foundation, in conjunction with the International Development Research Centre of Canada and 16 other sponsors, formed the Independent Commission for Health Research and Development to “*review the history, needs and opportunities for research that can improve health in the developing world.*”

The Commission set four goals for its two-year life span:

- (1) “produce an independent, comprehensive, expert analysis of current strengths, weaknesses and gaps in research and development activities concerning health problems in developing countries...*
- (2) promote action to fill gaps, enlarge existing activities, or otherwise strengthen research and development efforts and their links to field and community programs...*
- (3) define the needs for greater health research capacity in developing countries, with a special emphasis on Africa, and to propose means by which the needed capacity may be progressively achieved...*
- (4) consider the desirability, sponsorship and working methods for a continuing system of periodic assessments of research and development efforts concerned with health problems in developing countries...[in order to] determine priorities, increase the resources devoted to research and improving the effectiveness with which such resources are used.”*

The Commission’s final product, a report entitled Health Research: Essential Link to Equity in Development, was published in 1990. The Independent Commission had four recommendations:

1. Essential national health research conducted by all countries;
2. International partnerships to mobilize and focus scientific capacity;
3. Larger and more sustained financial support to supplement investments by developing countries; and
4. International mechanisms to monitor progress and promote the agenda of financial and technical support for research on health problems.

The Commission's findings inspired the Foundation's reconsideration of current grantmaking efforts and consideration of future efforts through this lens. Given the heavy emphasis of the Foundation's TDR Program on technology—primarily generated within the industrialized world—the Commission's recommendations challenged TDR staff to find new opportunities to focus on in-country capacity-building within the existing programmatic framework. This shift in focus—from the development and exportation of basic research to the fostering of research capacity—set the stage for the Foundation's applied work in Ghana and Tanzania.

Following the dissemination of the Commission's report, the Task Force on Health Research for Development was established to maintain international focus on ENHR by promoting, facilitating and supporting ENHR in countries that wish to undertake it; developing and evaluating longer-term mechanisms for the support of ENHR; and promoting synergism between research on global health problems and ENHR. Although the Foundation did not foresee a continuing role for itself with regard to the Task Force's work, the promotion of ENHR became a part of the goal-setting process within the TDR Program: *"We expect that our future work in control—support for applied research and training in operational research—will reflect the Commission's recommendation of increased support for ENHR and capacity-building in select countries"* (Cook, Mecaskey, Ehle 1992). ENHR also provided a framework as added rationale for undertaking the Health of School Age Children Program.

Although efforts to establish the Commission were not central to the pursuit of the TDR Program's disease-specific goals, the pursuit of the Commission, as well as the

results of this activity, had far reaching effects both within and outside of the Clark Foundation. The Commission was a concerted effort to gather the real “players” in international health to work in a complementary fashion to identify gaps in the field strategically. This process benefited each participant organization by providing data to inform their unique efforts as well as collaborative ones. Foundations have been criticized for being “too individualistic,” a disservice to each other and to their clients. The Commission’s work was predicated on the notion that what is called for, at times, is a systematic approach to identify gaps in the field and the strengths and weaknesses of the players on that field to enable each entity to do what they do best in the interest of the larger good.

A subsequent Foundation grant of \$200,000 supported further work on ENHR opportunities in Africa through the Task Force for Health Research for Development, which had been established to promote ENHR. Two additional research forums ensued; today, the Commission’s work is carried out by the Council on Health Research for Development (COHRED), based at the United Nations Development Programme office in Geneva (COHRED 2000). The Foundation's \$400,000 investment, combined with those from 11 other funders, created a long legacy that continues to the present in the form of the Global Forum for Health Research, convened to examine funding priorities and inequities between developed and developing countries. As one informant summed it up: *“This is Joe’s baby without question, no DNA test required!”*

VI. The Health of School Age Children (HSAC) Program (\$4.3 million, 1993-1998)

a. HSAC Program Context

One year before the development of Clark's strategic plan for schisto, a Brazilian physician coined the term "selective chemotherapy" to describe a control strategy for schisto, based on the fact that the distribution of worms varies in populations; thus, a more effective approach to morbidity control might be to focus on those most heavily infected. Participants of a 1979 conference in Bellagio, Italy reiterated that control should aim at markedly reducing intensity of infection through treatment and reduction of transmission, rather than through the total eradication of worms in individuals or populations; these findings led to the targeting of children because they tend to bear the heaviest burden of infection. In the next few years, this approach was evaluated in several small studies of *s. mansoni*, *s. japonicum* and *s. haematobium*, and endorsed by the WHO.

The cost-effectiveness and health effects of deworming received increasing prominence from the international health community during the 1980s. The United Nations Educational, Social and Cultural Organization took a particular interest in parasite control with regard to school-readiness and performance; the World Bank and UNDP were pursuing similar approaches to assessing the effects of helminths and their control in school children.

One of the TDR Program's early goals for the Schisto Program had been to focus on the quality, effectiveness and economic feasibility of control efforts. During the early years of the program, grants for epidemiology and control projects had focused on the collection and expansion of basic knowledge of the epidemiology, impact, morbidity, natural history, and the role of water in transmission. With these fundamental data in hand, the Program's focus shifted to issues of greater complexity designed to advance the field by building upon existing knowledge; these included epidemiological surveillance surveys, transmission dynamics and modeling, and early assessments of

chemotherapeutic control measures. Interest in chemotherapeutic approaches had garnered more funding through a series of grants in the mid-1980s to early 90s, including some for workshops and symposia on various aspects of control including cost-effectiveness, organization, management, and other operational research issues. In 1991, however, when the Schisto Program adapted the “geographic-centered” approach of the Foundation’s domestic programs into a “country-centered” effort, it focused on Ghanaian (West Africa) and Tanzanian (East Africa) control efforts.

That same year, Ghana’s Expanded Program in Chemotherapy (EPC) was established. The EPC focused on the treatment of school age children for intestinal helminths and schistosomiasis because prior research indicated that these children, a relatively neglected group, often bore a larger burden of parasitic disease. The concept was modeled by Dr. Donald Hopkins, of the Task Force for Child Survival at the Carter Center, after the WHO’s Expanded Programme on Immunization.

In August 1991, a meeting was convened in Bellagio, Italy by a number of public and private funders to review recent advances in expanded treatment programs for children and to make recommendations for program strategies. A broad international effort funded by the UNDP, WHO, the Wellcome Trust, and the Rockefeller, McDonnell and Clark Foundations among others, emerged from the meeting committed to improving the health of this age group through micronutrient supplementation (*e.g.*, Vitamin A capsule distribution) and health education in addition to deworming. This effort became known as the Partnership for Child Development (PCD). The PCD strove to establish and pilot test a model for parasitic disease control in four to six countries; PCD’s model was based, in part, on findings from research initiatives in Kenya funded by the Clark Foundation. Their aim was to evaluate the pilot intervention by documenting costs and benefits in the host countries, and to assess the likelihood of going to scale. In 1992, the Ghanaian EPC joined the PCD, and Ghana became one of the PCD’s four pilot countries. The Partnership also became “*the vehicle for [Clark’s] country-centered strategy of field-based operational research*” (Cook and Mecaskey 1994).

This was consistent with the Independent Health Commission's Report which had inspired TDR staff to reexamine its current and prospective efforts. As a result, the Foundation sought opportunities to focus on capacity-building, primarily through strengthening existing control programs. Integrated parasite control, focusing at least in part on schisto, was a natural segue for the TDR Program both operationally and materially.

b. Program Strategy and Plan Development

The Health of School Age Children Program was chosen from among a number of opportunities presented to the Advisory Committee and Board in 1994, including the health of displaced people, tuberculosis, sexually transmitted diseases, acute respiratory infection, and cardiovascular disease. The Program, designed to help build capacity, had school age children as the focus and operations research as the primary tool. The idea was to move developing countries forward by helping them to identify problems, and develop economically feasible and sustainable opportunities to improve their health care systems using existing tools. This represented a major shift in emphasis for the TDR Program.

The Program strategy architecture was guided by several lessons learned from preceding efforts in the three disease programs. First, there was an explicit recognition of the futility of vertical approaches (*i.e.*, single-disease programs) in the presence of limited resources and the need for integrated health services. Staff also saw that data were imperative to inform and help influence decision-making and policy formulation. The role of political will and self-determination posited that externally conceived and managed projects were doomed to failure, while programs that were designed and implemented by host-country nationals had a far better probability of being sustained and successful. Recognition of the importance of using data to inform policy also shaped the Program's contours. According to staff: *"the challenge for us is to nourish an understanding of what research can contribute to policy and to foster a demand for that*

knowledge.” The final lesson referred to the requirement for capacity-building endorsed by the Commission.

The Advisory Committee and Board deliberated the tension between essentially two foci—capacity-building/operational research and school age children—for more than a year. By May 1995, the Foundation had agreed that the program would focus on the health of school age children but incorporate a capacity-building component. The program was launched with an eye on developing a strategic plan within the first eighteen months of its implementation; this initial phase, characterized by the organization of country-specific steering committees and data collection, was intended to inform the strategic planning process.

Within a year, however, staff reverted to the original focus on capacity-building and diminished the emphasis on the health of school age children, after recognizing that *“making measurable changes in the health of school age children in two countries is unlikely in the short run and is truly a long term effort”* (Cook and Mecaskey 1996). The revised program would address institutional capacity-building and public health training (the curriculum for which would be informed from the results of operations research grants made in the prior year). By December of 1996, staff also backed away from this approach, citing the *“emergence of a major window of opportunity in trachoma control, coupled with awareness that progress will be slow at best in public health capacity-building in Tanzania and Ghana,”* and proceeded to outline an exit strategy for HSAC after a short period of “modest investment”.

Given that the HSAC portfolio was relatively narrow, and the main component—the PCD—had other means of support, Clark was able to execute a relatively seamless withdrawal by making some terminal grants to support analyses and publications of the findings from Tanzania and Ghana. It is unclear however, whether any other funder was able to “step-up-to the plate” with regard to the public health training initiative for Ghana and Tanzania.

c. HSAC Outcomes

Of all of TDR's endeavors, several key informants characterized this program as TDR's most diffuse effort and one with an "opaque" strategy guiding it. While Clark's activity in this area has been attributed as *"useful in getting helminth control on various agendas," ... "No one adequately appreciated how little Ministries [Health and Education] interacted with each other... The idea of intersectoral collaboration was an erroneous assumption."* Others indicated that the problems lay with the Partnership approach: *"The PCD has never been able to move from a research phase to a national program... There have been problems in scaling up at the country level. WHO and UNICEF have not been brought on as much at the regional/country levels, but have been at the international level."* Another informant felt that the PCD was ill-fated from the start: *"They designed a study that was so bad you could see it would produce nothing... the Bank was in its arrogant phase, tended to know it all, make judgements in house."* Another criticism was levied at PCD's *"blanket approach"* to the treatment of worms that have distinct epidemiological profiles and may require a more customized approach.

Conversely, the project is credited by one informant with creating momentum for other regions like Southeast Asia and the Western Pacific, which have been able to secure a regular budgetary post for worm control at WHO. In addition, the Program supported 27 related publications and informants generally felt that the operational research component made a good contribution to understanding the effects of helminths on anemia. *"With regard to its sustainability though, as soon as outside funding stops, it will collapse."*

Another important, but unintended contribution of the Program was the experience staff gained in negotiating with multiple partners, in this case particularly, SmithKline Beecham with regard to pricing for an important antihelminthic drug for the program. Staff later utilized this knowledge of two-tier pricing schemes to help orient negotiations with Pfizer for the donation of Zithromax[®] to combat trachoma.

VII. The Importance of People and Processes

The shape and trajectory of the Foundation's Developing World/TDR Program, as in all of the Foundation's programs, ultimately rested on decisions made by the Board in executing its stewardship role. These decisions were based in large part on recommendations of program staff and their advisors, within the context of the Foundation's overarching mission and aims. This places a critical emphasis on the importance of the program directors' orientation, experience, knowledge, talents and skills, and on the processes used for interchange between Board members and program directors.

Perhaps more than in other Foundation programs, however, the highly technical nature of tropical disease research posed significant challenges for Board members in exercising their stewardship role, and for staff and advisors in providing the Board with an informed basis for making decisions.

The selection of Dr. Hoffman to create the Developing World Program appears to have reflected an interest in taking a managerial, entrepreneurial approach. His training in biophysics and consulting experience in a developing country provided the kind of orientation, experience, talent and skills sought. Because he was not an expert in tropical diseases, and because his systems approach to management involved bringing leading scientists into the planning process, outside experts exerted a major influence on helping him chart the initial scientific direction and plans. Nonetheless, Dr. Hoffman was not a "captive" of his advisors' enlightened self-interest. He combined their recommendations concerning which disease to target and what scientific leads to follow with his interest in incorporating the new science of molecular biology. The means he chose, in contrast to the investigator-initiated process of the NIH, were more akin to those used in industry and consulting: goal directed, sequential, and bounded by anticipated timeframes.

Dr. Cook was recruited with research expertise in the field, in-country experience working on a (Rockefeller) Foundation-supported grant, prior experience working at the

NIH, and a method of operation that has been cited as truly collaborative. The Foundation chose him to lead the program based on this perspective and experience. He has been viewed by many as a master in determining strengths of potential collaborators and crafting roles for them accordingly, and in navigating complicated international relationships. According to one informant, Dr. Cook had the *“management capacity to actualize his vision—this makes all the difference—look at Churchill, he was a high school dropout.”* Dr. Cook’s acumen has earned him the respect and trust of colleagues from every sector the Foundation’s work has embraced. One member’s comment during a Board meeting speaks volumes to this: *“I am supporting Joe’s recommendation on this because I trust him.”* Similarly, as Dr. Coleman recently commented, *“I have faith in people who can explain in plain English what they are doing. Joe was the model of a person who could tell you why something was important. My confidence in the Program was based on my confidence in Joe. I never once suspected that he overstated accomplishments. He was modest and solid.”*

Major vehicles for the Board to gain information and advice were the Strategic Plan and regular Program Updates, participation by designated Board members in Advisory Committee meetings, memos from the Foundation presidents and TDR Program directors, and occasional site visits to in-country projects. With the establishment of the ITI, the level of direct Board involvement has escalated substantially, with three of the Foundation’s Board members serving on the ITI Board.

The Developing World Program Strategic Plan oriented the Board to goals and objectives, and a timetable for achieving benchmarks. As the Program evolved into TDR, the Strategic Plan remained the basis for gauging progress. Program Updates prepared by staff became the primary vehicle for regularly informing the Board on the status of grantmaking efforts. When Oncho and Trachoma were recommended as new program areas, the rationale, description and preferred approach were conveyed through a Program Update. Through the Updates, staff tracked progress toward achieving benchmarks and provided recommendations for mid-course refinements or new directions.

Written for a non-scientific audience, these Updates clearly described the target diseases and explained the rationale for pursuing specific avenues. They provided an assessment of successes and disappointments and a thoughtful discussion of problems and plans for addressing them. They also described new opportunities and recommendations for pursuing those. Board decisions at key program junctures were often precipitated and informed by the Program Plans and Updates. By having vested in the Task Forces the responsibility for determining technical direction, choosing competitive grants program awardees, and coordinating research resources, the Board could concentrate on determining if results were on target rather than having to weigh in on technical decisions. Dr. Coleman recently stressed that when Boards are overseeing programs that are based on highly technical information, *"Boards should never be shy about asking. Boards cannot be afraid to ask when they don't understand. Joe's success in communicating with the Board and me was because he explained things with modesty, directness, simplicity...I never doubted that we had full support of the Board. That was attributable to Joe."*

The composition and mission of the TDR Advisory Committee, as well as its relationship to the Board and staff, were factors of central importance in guiding the Program. In a 1980 memo to the Board, President Coleman addressed what he viewed as the Advisory Committee's mission and role: *"...to bring to our Trustees that kind of broad oversight and independent, knowledgeable review that was unlikely to come from ..the board who are perhaps too close to what's going on to maintain perspective... New voices, new ways of looking at things, a mixture of expertness in the specific field and of more general knowledge...Naturally, we hoped for polite people on the committees. But more, we hoped for toughness, independence, openness and vision."*

The selection of good candidates for the Committee was a challenge, particularly with regard to schisto. At the time, staff felt that the size of the field limited the choices, and although it was considered less than optimal to have grantees serve on the Advisory Committee, this seemed unavoidable if staff were to secure the "best and brightest" as

advisors. President Coleman voiced concerns about this potential conflict with reference to both the Foundation's domestic and international programs. *"We need to re-think the question of committee make-up...Find ways to resolve possible overlapping roles of committee members and grantees. In the case of Schistosomiasis, we have no alternative (nor do we want one) but to include some grantees, given the fact that so many of those who do know about the disease are our partners."* Internal documents suggest that this issue continued to resurface over the years, and although President Coleman's earlier inclination was that advisors *"would never be so taken in by our money our commitments, or experience or our style that they would yield an ounce of their critical acumen,"* nonetheless, he noted that *"Occasionally committees seem to have forgotten their roles as overseers and constructive critics of what we're doing. Punches have been pulled, tough issues ducked, and information-sharing and mutual admiration have been substituted for hard, purposeful discussion on our means and ends."*

Participation by designated Board members in Advisory Committee meetings was a direct means for those members to obtain a sense of Program progress and barriers. The nature of Board participation has changed over time due to differences in philosophy and lessons learned from experience. Under President Coleman's tenure, Board members were involved in the discussion between staff and advisors, and then met privately with the advisors. *"...we probably ought to find a way by which each committee can report directly and privately to our trustees. The committees are here to serve the trustees. That means there should be times when they can share, in confidence, their overall views of how well we in the staff are doing our jobs, how appropriate our priorities are, and where we ought to consider going next. Sometimes this sharing can be in the form of a brief written report at a meeting's end. Other times it should be in a face-to-face meeting between trustees and advisory committees alone."* According to recent comments from Dr. Coleman, *"I find people in whom I have confidence, and then tell them to go ahead, but tell me what you're doing. Let me hear your advisors' comments...It did work for me to hear advisors directly. I learned a lot from them."*

According to one informant, *"No one was comfortable with Jack Coleman's approach of using the executive session as a sort of 'report card' on staff. No one thought it was a good way of doing business."* One of Peter Bell's first changes as president was to eliminate this private session. *"It was clear to me that advisors should be advisory to staff. But Board members could sit in and learn, and that was useful."*

While informants were generally in agreement that most vehicles for informing Board members worked well in enabling them to make decisions, informants differed widely on the utility of direct participation in Advisory Committee meetings. Some informants questioned the utility of having Board members participate in advisory sessions. *"Foundations should let information flow up to the Board, and Foundation staff should have the responsibility for ensuring that the information is put together well,"* one informant stated. A Board member emphasized the utility of that approach for the Board. *"Technology is not transparent. We had to rely on experts for their technological judgment and integrate that into our governance process. The experts, advisors and staff were very skillful in helping the Trustees understand the issues well enough to be good stewards."*

According to another informant, *"People wouldn't say in open meetings that they disagreed with something, for fear that Board members might misunderstand their import or implications."* Several informants expressed this view in several ways. One Board member stressed that the concept of the Board having direct involvement was a good one, but didn't work as hoped. *"The Board is composed of 'generalists,' people who are not specifically expert in any of the Foundation's fields. The Board felt it could function better if its members did not represent a particular constituency. Instead, Board members were looking to bring experts into the orbit, and to ask them to 'think of themselves as Trustees' and look at programs the way a Trustee would. It was a great concept but it didn't work in practice. Both staff and advisors were uncomfortable with it. Without some direct involvement with advisors, though, we close an important window...Trustee participation in Advisory Committee meetings was a way to keep the windows open, to enable the Board to see if things were on track."*

Occasionally, the Foundation president or TDR Program director would communicate key issues to the Board through a memo sent in advance of the next scheduled meeting. Memos covered a range of issues. For instance, a February 1979 memo from Dr. Cook described Foundation patents for schistosomiasis-related products that were of possible commercial interest, while a 1981 memo discussed Dr. Cook's thoughts about what factors should be considered in determining whether to exit from schisto.

An additional means of input was the occasional participation by a few Board members on a site visit to grantees in major tropical disease-endemic countries. This first-hand exploration of issues and accomplishments directly with grantees would be chronicled in site visit reports written by staff, and commented on directly by involved members in subsequent Board meetings. The effect was captured by Dr. Coleman in recent comments: *"Not long before I left, Joe took me and John Emery and Lucy Nesbeda to Africa (Egypt, Sudan, Kenya). To go into a village and have students lined up and singing a song of thanks to the Foundation because they knew that they weren't going to have to suffer like their parents did, then you knew you were doing the right thing. It was a searing experience."* An often-reported observation by Board members was how well-regarded Dr. Cook was by those grantees and the ministries of health and other in-country officials who worked with them.

VIII. Lessons Learned

Several useful lessons have emerged from the TDR Program's 25 years of experience. Presentation and discussion of these lessons is undertaken with a healthy respect for the maxim that *"hindsight is always 20/20."* As Mr. Emery cautioned, *"trying retrospectively to recreate the path from TDR to ITI as a map for the future would be like cold fusion. Serendipity played a role."*

Although these lessons have arisen from an international program focus, and from the relatively technical field of tropical disease research, they address some fundamental aspects of grantmaking that may provide helpful insight for the Foundation's new approach to helping to strengthen the field of youth development. For the most part, they can be distilled into six key elements. A few examples are used within each to illustrate the points.

- 1. Strategic planning provided an essential framework. It worked best, however, when assumptions were made explicit, and when the planning process was flexible enough to take advantage of opportunities and to adjust to a constantly changing environment.**

The strategic plans for each of the TDR programs served several essential purposes. They provided a focus and direction that oriented the Board, staff, and grantees to the goals, objectives and means for each of the programs. They also provided a mechanism for scientific leaders to contribute to the planning process, and to share "ownership" of the approach. Nonetheless, assumptions--both scientific and operational--were not always made explicit. This made it more difficult to challenge the "conventional wisdom" and the assumptions underlying it, and to adjust the planning accordingly.

- Scientists assumed that resistance to the drug praziquantel would occur over time [diminishing the role of drug therapy in schisto control efforts]. This provided a

rationale for pursuing a schisto vaccine as essential to long-term disease control. Resistance has not yet occurred to a significant degree, however. It is unclear whether this assumption was reexamined during the extended 13-year commitment to vaccine development through 1994.

- While plans relied on the likelihood that industry would undertake further development and production of vaccines once promising candidate antigens were identified, this crucial assumption did not seem to have been investigated explicitly. NIAID is currently encountering difficulties in stimulating industry interest in developing experimental vaccines to test the several antigens identified to date, most of which were initially explored by Clark Foundation grantees.
- The projected timeline for vaccine development was estimated early in the evolution of molecular biological and immunological tools. It is not clear whether a critical assessment of these tools' applicability to vaccine development was reevaluated over time as the complexity of the underlying basic science became better understood. Experience, such as that revealed by NASA's strategy to land a man on the moon, suggests that a strategically directed research agenda may work best when the essential scientific components are known and mainly need to be coordinated. The TDR Program's directed approach was a much higher risk since it appears to have been ahead of the "readiness" of the science.
- Nonetheless, calculated risk-taking can play a crucial role in philanthropy, which has the "luxury" of resources regardless of program outcomes. For instance, risk-taking in the School Age Children's Program did not result in anticipated program outcomes, but it did produce some unanticipated benefits when staff explored prospects for a two-tier pricing system for SmithKline's albendazole, the recommended drug treatment. The knowledge and experience gained through this negotiation process was of tremendous advantage when the opportunity to collaborate with Pfizer arose. A foundation colleague summed it up aptly: *"In*

the grantmaking business, if all your programs succeed, then you're not taking enough risks.”

- Assumptions were made explicit in the “rifle shot” approach of the oncho vaccine program. Staff and the Board made the explicit decisions to pursue a narrowly focused effort, which was a high risk/high yield approach. Narrow approaches run the risk of becoming a funding “sink-hole,” particularly for niche players, yet unanticipated successes or even incremental products can justify the investment in the end.
- Additionally, the Oncho Program's initial plan--which assumed that essential research resources were available--was challenged by workshop participants. This resulted in development of a highly coordinated research resource capacity that has been credited with greatly accelerating progress on differentiating protective from deleterious antigens.
- The strategic updates late in the Trachoma Program reflected a plan to phase out of the sole remaining area of epidemiology and control because research had established the potential utility of the SAFE program, which was being incorporated into the WHO's GET2020 Initiative. Yet, TDR Program staff recognized the exciting potential of Pfizer's Zithromax[®] to improve the antibiotic component of the program, and rapidly and effectively catalyzed clinical trials that demonstrated its superiority over existing products. This ability to recognize and foster opportunity, and the flexibility to adjust plans accordingly to coordinate the trials and to establish a partnership with Pfizer, has been a striking advance for the field.
- The Health of School Age Children Program was an attempt to merge the notion of geographic focus, a domestic program theme, with the notion of helping to build in-country capacity. The Foundation assumed a shared theme among domestic and international programs would work, however, this approach forced

artificial similarities that were not practical or in the best interests of the participating countries. Problems in developing necessary in-country relationships and the support of major stakeholders emphasized the mismatch between the Foundation's objectives and the countries' internal priorities.

2. Assessing, or "field testing" innovations to determine if they work in practice provided vital feedback for refinements.

Undertaking development of disease control tools, such as drugs and diagnostic agents, was most successful when it was followed by operations research to determine optimal means for implementation. This has critical implications for sustaining field-building efforts.

- The rationale for developing a diagnostic tool for schisto was to improve surveillance outcomes and targeting of treatment with praziquantel. But, the test developed was underutilized, largely because the cost of praziquantel failed to decline to affordable levels, rendering the test irrelevant. This and other information on praziquantel did, however, lead the TDR Program to support efforts to make a cheaper version of the drug.
- Operations research was used to assess the efficacy of surgery undertaken by nurses in correcting trichiasis (inward-turning eyelashes) in trachoma, followed by nurses training. Subsequent studies have established the effectiveness of this surgical intervention in preventing blindness from trachoma.

3. Formal, external evaluation was rarely used, and the TDR Program missed an opportunity for information that might have helped guide or alter its course.

The TDR Program did not involve evaluators prospectively, during program design and implementation, and it appears that staff did not develop an explicit

understanding of whether, and if so how, desired outcomes were to be measured. By failing to define operational definitions of expected Program outcomes, it is likely that grantees did not understand fully the criteria that would be used to determine if they should continue to be funded. Instead, the TDR Program used progress toward scientific benchmarks. While this provided critical information on tactics, it did not assess overall direction and relevance within a changing environment.

- When scientific objectives were not met, there may have been a tendency to focus on redefining *means* rather than on reassessing *objectives*. In the one formal evaluation undertaken, of the Oncho Program, outside evaluators' assessment produced a shift in the Program's direction to concentrate on key areas of opportunity that would advance the field and position it to garner competitive funding from other sources as an exit strategy.
- The absence of formal evaluations places even greater reliance on *post hoc* analyses of quantitative data reflecting the status of specific aims. The process of an evaluation, however, can be valuable in revealing qualitative aspects that may be otherwise overlooked. Even simple outcomes analyses can provide useful ongoing status updates, such as the schisto immunology literature review conducted in 1986. Although this report provided strong evidence of the contribution of Foundation-funded grantees to the field's scientific literature, such studies were rare. Additionally, there was no explicit tracking and no attempt made to count the number of new scientists attracted into tropical disease research, even though this was an explicit objective of the TDR Program.
- Independent verification, through outside evaluations, can be an important adjunct to information available to the Board to carry out its stewardship role, particularly in highly technical fields. Board members have relied upon the excellence of and trust in the TDR Program directors, and on input from program advisors who are recognized to have to balance their self-interest against "objectivity." This

process is generally acknowledged to be imperfect but largely effective. Program evaluations will not perfect the situation, but would be additive.

- Planning and evaluation of the ITI's activities is based, in part, upon epidemiological data provided by each of the pilot sites. Strategic plans should include quality control measures to assure the availability and reliability of necessary data. Because the ITI is in an early stage of development, serious consideration should be given to developing and undertaking a prospective evaluation.
- 4. With experience, the exit strategies became progressively better developed and implemented.**

Staff recognized over time that exit strategies were needed to help strengthen the capacity of researchers to build upon Foundation-funded gains and to progress in the absence of continued funding. The ITI may represent the first exit strategy to identify fully the factors that are both necessary and sufficient for continuing to progress toward the goal(s), and by determining feasible means to assist these efforts to become self-sufficient. As such, the ITI may provide an important model for the Foundation's newly evolving institution- and field-building approach.

- While schisto researchers were grateful for the gradual withdrawal from the field, the only mechanism developed to facilitate continued progress on a schisto vaccine was establishment of the Schisto Vaccine Task Force and short-term support to WHO to sponsor it. This was insufficient to promote continued progress. NIAID and the European Union have continued to support schisto vaccine research, but have not been successful in finding industry sponsors to undertake development of promising antigens. Thus, neither the public nor private sectors has created conditions necessary to sustain the work.

- Lessons learned from the Schisto Program informed development of a strong exit strategy for the Oncho Vaccine Development Program. That Program's exit was facilitated by its grounding in a progressively more tightly focused strategic plan, and the early creation of mechanisms to produce and provide research resources and to foster collaboration. Nonetheless, the Foundation recognized that even while these advantages would put the researchers in a stronger position to compete for NIH funding, continued progress on an oncho vaccine was not assured. While in the short-term funding for oncho vaccine development will decline, the potential for sustained progress is greater than it was for schisto. Evidence of this includes newly created funding sources and organizational linkages, current NIAID funding of key investigators, recent scientific “breakthroughs,” and the exchange facilitated by the OnchoNet website. It is clear, however, that the ultimate goal of a safe and effective vaccine for human use lies far in the future, and will be difficult to achieve (as with schisto), without active participation of industry.
- Initially, the exit strategy for trachoma was similar. For the vaccine work, the strategy was to leave future research efforts to the NIAID where they might be incorporated into ongoing chlamydia research on genital tract and lung infections. But with the promising early studies of Zithromax[®] in treating trachoma, the exit strategy took a major turn and focused on helping to establish the drug's efficacy as part of the SAFE strategy. It then progressed to development of a partnership with Pfizer to design and implement a drug donation program as part of this strategy. This institution and field-building effort will become dependent on other funding partners, on effectively managing complex relationships with a host of international and in-country agencies and NGOs, and on continued commitment of Pfizer to donate the drug for the long-term. An assessment of these and other factors necessary for sustaining progress toward trachoma control would be a valuable contribution to the field of field-building.

- For instance, the ITI has, in essence, “captured the field” by virtue of its exclusive arrangement with Pfizer to utilize Zithromax[®] in the elimination of blinding trachoma. However, Pfizer will lose its worldwide patent for Zithromax[®] in 2001 and its U.S. patent in 2005. What are the long-term implications of these eventualities for Pfizer's continued donation and for funding from other sources? If necessary, will ITI have the funding to responsibly exit the field?

5. Strong, clearly-defined working relationships were an essential hallmark of successful TDR Program activities.

The TDR Program demonstrated that successful collaboration required knowing the strengths, limitations, public perception, and culture of collaborating organizations, and designing collaborations accordingly. This has critical implications for institution- and field-building strategies. Providing pilot or small-scale grants to potential collaborators was an often used and effective means for assessing their strengths and limitations.

- Strategic alliances with the WHO were based on first-hand experience with WHO's Tropical Disease Research and Blindness Prevention Programmes, the context within which they operated, and on an understanding of which goals the two organizations shared, or conversely, what unshared goals might be complementary. For instance, knowing the financial and political factors that limited WHO/TDR's long-term commitment to oncho vaccine development created an opportunity for the Foundation that its colleagues at WHO welcomed.
- Pilot grants provided to collaborating organizations helped identify strengths that were later called upon in larger scale efforts. This included the NGO Helen Keller International's expertise, flexibility, and strong networking in the field that were revealed by earlier grants and later called upon to provide the initial home of the ITI. When establishing multi-party alliances, the TDR Program evidenced

knowledge of the partners' strengths, organizational capacity, and mission and balanced these against weaknesses and potential conflicts.

- Important to the successful partnership with Pfizer in creating the ITI partnership was a well-honed understanding of the shared goals of the two organizations, and of an appreciation of one another's objectives and the rationale for these, according to the recent Harvard Business School case study (Barrett, Austin, McCarthy 2000). As one Board member indicated, this partnership is predicated on the common goal of preventing blindness from trachoma, and the economic issues that usually contribute to the breakup of joint ventures is not likely to be present.
 - In contrast, in the Health of School Age Children's Program, the Foundation's lack of understanding of the partners' capabilities, objectives and means of operations hindered collaboration and limited the Program's success.
- 6. The TDR Program's entrepreneurial approach to grantmaking sought to create sustainable conditions, in the absence of a viable private sector market, and this may stimulate ideas for working with industry to help build capacity in other fields.**
- In one approach, the Foundation sought to "take matters into its own hands" by supporting research on the development of a cheaper alternative to praziquantel for treatment of schistosomiasis.
 - In another approach, the Foundation developed its own industrial process, by providing support to industry (Parke-Davis) to work on drug development directed by the Foundation, and grants to academic institutions to carry out carcinogenicity and animal testing functions that are an essential part of drug development.

- The Foundation took out patents on grantee product therapeutic and diagnostic innovations, to help facilitate industry willingness to further develop, produce and market products by barring competition from cheaper copies.
- In the case of ITI, the Foundation first catalyzed the studies necessary to demonstrate efficacy, and then developed a working partnership with Pfizer to develop, coordinate and assess drug donation incorporated into the SAFE strategy. This latter approach may prove to be a hallmark in private sector for-profit, not-for-profit ventures.

APPENDIX A
Edna McConnell Clark Foundation
Decision Makers 1974- 2000

DATE	ADVISORY COMMITTEE BOARD of TRUSTEES	
1974 James F. Henry, President	John Hannah, J. George Harar, Ken S. Warren	H, J, &VA Clark, Emery, Henry
1975	John Hannah, J. George Harar, Ken S. Warren	H, J, &VA Clark, Emery, Henry
1976	John Hannah, J. George Harar, Ken S. Warren	H, J, &VA Clark, Emery, Henry
1977 John R. Coleman, President		H, J, &VA Clark, Coleman, Emery, Kennedy
1978	Bradley, Hoffman, Phillips SM, Stein	H, J, &VA Clark, Coleman, Emery
1979	Bradley, Hoffman, Phillips SM, Rosenfield, Stein	H, J, &VA Clark, Coleman, Emery
1980	Bradley, Hoffman, Phillips SM, Rosenfield, Stein	H, J, &VA Clark, Coleman, Emery, Wilson
March 1981	Bradley, Hoffman, Phillips SM, Rosenfield, Stein	H, J, &VA Clark, Coleman, Emery, Wilson
October 1981	Bradley, Colley, Mahmoud, Rosenfield (chair), Stein	H, J, &VA Clark, Coleman, Emery, Wilson
May 1982	Bradley, Colley, Mahmoud, Rosenfield, Stein	H, J, &VA Clark, Coleman, Emery, Wilson
October 1982	Colley, Guerrant, Jordan, Mahmoud, Rosenfield	H, J, &VA Clark, Coleman, Emery, Wilson
April 1983	Alleyne, Colley, Guerrant, P. Jordan, Adel Mahmoud, Rosenfield,	H&J Clark, Coleman, Emery, Nesbeda, Wilson
October 1983	Alleyne, Colley, Guerrant, Jordan, Mahmoud, Rosenfield	H&J Clark, Coleman, Emery, Nesbeda, Wilson
April 1984	Alleyne, Colley, Guerrant, Jordan, Mahmoud, Rosenfield	H&J Clark, Coleman, Emery, Nesbeda, Wilson
October 1984	Alleyne, Grayston, Guerrant, Jordan, Rosenfield	H &J Clark, Elliott, Emery, Nesbeda, Rothschild, Weinberg, Wilson
April 1985	Alleyne, Grayston, Guerrant, Jordan, Rosenfield, Ottesen	H &J Clark, Elliott, Emery, Nesbeda, Rothschild, Weinberg, Wilson

Edna McConnell Clark Foundation
Decision Makers 1974- 2000
(continued)

December 1985	Alleyne, Dawson, Grayston, Mahmoud, Ottesen, Rosenfield	H &J Clark, Elliott, Emery, Nesbeda, Rothschild, Weinberg, Wilson
April 1986 Peter Bell, President	Alleyne, Dawson, Grayston, Mahmoud, Murray, Ottesen, Rosenfield	Bell, H &J Clark, Elliott, Emery, Nesbeda, Rothschild, Weinberg, Wilson
October 1986	Dawson, Grayston, Lucas, Mahmoud, Murray, Nussenblatt, Ottesen	Bell, H &J Clark, Elliott, Emery, Nesbeda, Rothschild, Weinberg, Wilson
March 1987	Dawson, Grayston, Hopkins Lucas, Murray, Nussenblatt, Ottesen	Bell, H &J Clark, Elliott, Emery, Nesbeda, Rothschild, Weinberg, Wilson
October 1987	Dawson, Donelson, Hopkins, Lucas, Murray, Nussenblatt, Ottesen	Bell, H &J Clark, Elliott, Emery, Nesbeda, Rothschild, Weinberg, Wilson
April 1988	Dawson, Donelson, Hopkins, Lucas, Murray, Nussenblatt, Ottesen	Bell, H &J Clark, Days, Elliott, Emery, Nesbeda, Rothschild, Weinberg
October 1988	Donelson, Hopkins, Lucas, Nussenblatt, Ottesen, Taylor, Wirth	Bell, H &J Clark, Days, Elliott, Emery, Nesbeda, Rothschild, Weinberg
April 1989	Donelson, Hopkins, Lucas, Nussenblatt, Ottesen, Taylor, Wirth	Bell, H&J Clark, Days, Elliott, Emery, Nesbeda, Rothschild, Weinberg
October 1989	Donelson, Lucas, Hopkins, Nussenblatt, Ottesen, Taylor, Wirth	Bell, H&J Clark, Days, Elliott, Emery, Nesbeda, Rothschild, Weinberg
March 1990	Donelson, Hopkins, Lucas, Ottesen, Taylor, Thylefors, Wirth	Bell, H&J Clark, Days, Elliott, Emery, Nesbeda, Rothschild, Weinberg
October 1990	Donelson, Lucas, Martinez- Palomo, Ottesen, Taylor, Thylefors, Wirth	Bell, H&J Clark, Days, Elliott, Emery, Nesbeda, Rothschild, Schmultz
April 1991	Lucas, Martinez-Palomo, Ottesen, Taylor, Thylefors, Wirth	Bell, H&J Clark, J.Clark Jr., Days, Elliott, Emery, Nes- beda, Rothschild, Schmultz

Edna McConnell Clark Foundation
Decision Makers 1974- 2000
(continued)

September 1991	Lucas, Martinez-Palomo, Ottesen, Taylor, Thylefors, Wirth	Bell, H&J Clark, J. Clark Jr., Days, Elliott, Emery, Nesbeda, Rothschild, Schmultz
April 1992	Donelson, Jamison, Lucas, Martinez-Palomo, Sommer, Thylefors	Bell, H&J Clark, J. Clark Jr., Days, Elliott, Emery, Nesbeda, Rothschild, Schmultz, Wooden
September 1992	Donelson, Jamison, Lucas, Martinez-Palomo, Sommer, Thylefors	Bell, H&J Clark, J. Clark Jr., Days, Elliott, Emery, Nesbeda, Rothschild, Schmultz, Wooden
March 1993	Bloom, Donelson, Jamison, Krogstad, Martinez-Palomo Sommer	Bell, H&J Clark, J. Clark Jr., Days, Elliott, Emery, Nesbeda, Proctor, Schmultz, Wooden
October 1993	Bloom, Donelson, Jamison, Krogstad, Sommer, Toubia	Bell, H&J Clark, J Clark Jr., Elliott, Emery, Nesbeda, Proctor, Schmultz, Wooden
March 1994	Bloom, Donelson, Jamison, Krogstad, Sommer, Toubia	Bell, H&J Clark, J Clark Jr., Emery, Nesbeda, Proctor, Schmultz, Wooden
November 1994	Bloom, Donelson, Jamison, Krogstad, Sommer, Toubia	Bell, H&J Clark, J Clark Jr., Emery, McKee, Nesbeda, Proctor, Schmultz, Wooden
May 1995	Bloom, Hsiao, Krogstad, Nyi Nyi, Sommer, Toubia	Bell, H&J Clark, J Clark Jr., Emery, McKee, Nesbeda, Proctor, Schmultz, Wooden
October 1995 (CFO interim Pres)	Bloom, Hsiao, Krogstad, Nyi Nyi, Sommer, Toubia	H&J Clark, J Clark Jr., H.L. Clark, Emery, McKee, Nesbeda, Proctor, Schmultz, Wooden

Edna McConnell Clark Foundation
Decision Makers 1974- 2000
 (continued)

April 1996 Michael Bailin, President	Foster, Gardiner, Hsiao, Nyi Nyi, Sommer, Toubia	Bailin, H&J Clark, J Clark Jr., H.L. Clark, Emery, McKee, Nesbeda, Proctor, Schmultz, Wooden
November 1996	Gardiner, Hsiao, Nyi Nyi, Sommer, Toubia	Bailin, H&J Clark, J Clark Jr., H.L. Clark, Emery, McKee, Nesbeda, Proctor, Schmultz, Wooden
May 1997	Gardiner, Hsiao, Nyi Nyi, Sommer, Toubia	Bailin, H&J Clark, J Clark Jr., H.L. Clark, Emery, McKee, Nesbeda, Proctor, Schmultz, Wooden
October 1997	Henderson, Nyi Nyi, Sommer	
March 1998	Henderson, Nyi Nyi, Sommer	

APPENDIX B

Narrative Timeline Of Important Events

- 1972: Robert F. Goheen, EMCF President. Recommendation to Board to create an international program.
- 1973: December Board, recommendation adopted. Aims: Developing World Program with tropical disease emphasis. Efforts to broaden into other areas approved longer term. FY73 funding was \$350k prior to definition of program objectives.
- 1973: Two new schisto drugs approved by FDA for adult worms.
- 1974: James (“Jim”) F. Henry, EMCF President.
- 1974: (March) Board approves recommendation by workshop participants to concentrate on schisto because of importance of disease and opportunity it presents. Rationale: 200M people affected, spread by development projects, some important groundwork done, offers point-of-entry opportunity (few major funders of comparable size funding this area). First schisto grants awarded in June, 1974.
- 1974: (March-November) Strategic plan for research developed, program officially announced, contacts initiated with WHO, pharmaceutical companies, most labs in US, UK and some LDCs. Funded 15 grants for \$1.96M, FY74.
- 1974: WHO becomes Executing Agency for Oncho Control Program (OCP).
- 1975: WHO, UNDP, and WB organize and fund jointly the WHO Special Program for Research and Training in Tropical Diseases (WHO/TDR) to “*develop new methods of preventing, diagnosing and treating selected tropical diseases and methods that would be applicable, acceptable and affordable by developing countries.*” Program also aims to strengthen—through training and institutional support—capability of LDCs to undertake research to develop new disease control technologies. Six disease groups: malaria, schisto, filarials, trypanosomes, leishmaniasis, leprosy. [TDR has five advisory groups: a Scientific and Technical Advisory Committee, Joint Coordinating Board, Steering Committees, Scientific Working Groups and Research Strengthening Group].
- 1975: (May) Foundation provided 2-year consulting agreement for Dr. Hoffman as interim director until replacement found.
- 1975: (October) Dr. J.S. Lehman takes over as Director of Developing World Program.
- 1975: Monoclonal antibody techniques introduced.

APPENDIX B
(continued)
Narrative Timeline Of Important Events

- 1976: (October) Re-evaluation of strategic plan. Patent applications filed for Niridazole and immunologic test for schisto diagnosis.
- 1976: (November) Jimmy Carter, elected U.S. President.
- 1977: (June) John R. (“Jack”) Coleman, EMCF President. Developing World Program renamed Tropical Disease Research Program.
- 1977: (September) President Coleman proposes EMCF establish its own public relations effort rather than continue to rely on outside consulting firm.
- 1977: (October) Bellagio conference on “schisto state of the science,” co-sponsored by Rockefeller Foundation and EMCF.
- 1977: (October) WHO declares smallpox eradicated.
- 1977: (November) Bellagio recommendations to remain in schisto presented to EMCF Board.
- 1978: (March) Executive session of Board to discuss future of TDR program, following Dr. Lehman's death.
- 1978: (April) Meeting held on schisto drug development opportunities/challenges. (Pfizer's oxamniquine and Bayer's praziquantel on market and in wide use.)
- 1978: (July) TDR Advisory Committee recommends continuation of TDR Program under new leadership.
- 1978: (September) President Coleman appoints Dr. Joe Cook as TDR director, to begin November, 1978.
- 1978: Alma-Ata International Conference on Primary Health Care. Dr. Halldan Mahler, Secretary General of WHO urges “Health for All by 2000”.
- 1978: Annual report TDR statement by Dr. Cook describes shift from lab to field, resulting from findings of joint Clark-Rockefeller workshop that pointed to improvements in control methods meriting further investment.
- 1978: TDR/OCP/Merck joint animal trials for ivermectin.
- 1979: (September) Schisto Packet ended after two published issues.

APPENDIX B
(continued)
Narrative Timeline Of Important Events

- 1979: Schisto spending worldwide up to \$7M/year.
- 1979: (December) Grant to study costs of anti-schistosomiasis drugs, and prospects for developing joint purchasing arrangement for governments and bilateral aid agencies.
- 1980: (January) Merck decides to proceed with Phase I trials for ivermectin.
- 1980: (February) President Coleman discusses with Board clarifying role of advisory committees, improving methods for gaining advice on whether programs going in right direction, and when to change direction.
- 1980: (November) Ronald Reagan, elected US President.
- 1980: *Schisto Update* in circulation and considered to be meeting real need.
- 1980: Praziquantel and oxamniquine recognized to be in wide use for schisto treatment; staff recognizes need to shift support away from drug development.
- 1981: (February) Dr. Cook begins appointment on NIAID National Advisory Council.
- 1981: (April) President Coleman raises question of whether to put 25 percent of schisto funding into another disease, increasing to 50 percent the following year. Advisory Committee reviews potential new directions for TDR. Options include: amoebiasis, leishmaniasis, pulmonary disease in infants and children.
- 1981: (September) Dr. Cook recommends to President Coleman that schisto funding be reduced 10 percent, but that EMCF continue immunology work and assess whether control efforts working, with further reduction totaling 25 percent in four to five years.
- 1981: (September) Grant to explore simplified method for synthesizing praziquantel, as an opportunity to provide the drug at a reduced price.
- 1981: (December) President Coleman looks for potential common thread(s) for the three domestic programs.
- 1981: AIDS syndrome identified by Centers for Disease Control.
- 1982: Subject of withdrawal from schisto and program expansion raised with AC.
- 1982: (March) Foundation hires new director of communications.

APPENDIX B
(continued)
Narrative Timeline Of Important Events

- 1982: (December) Grant to NIH to support a molecular biology post-doc working on immunology. (NIH/FAES incorporated in 1959 as non-profit by a group of NIH investigators to promote advanced education for investigators and to serve as fiscal agent for outside funds awarded for NIH intramural scientists' work.)
- 1983: (April) Board proposal for schisto withdrawal and programmatic expansion approved, to include the two major infectious causes of blindness—oncho and trachoma. Refugee health care, migrant population health, leishmaniasis, and ARI explored but declined. Grants approved to convene workshops to develop research agenda in 1984-5 for the two diseases.
- 1983: (June) Dr. Cook indicates he is dropping support for development of live attenuated vaccines. Will concentrate on molecular biology approaches to vaccine, developing protective antigens using monoclonal antibodies, and recombinant DNA to produce adequate amounts of the protective antigens.
- 1983: (November) Board members split on whether to withdraw from schisto quickly or slowly and deliberately. Dr. Cook summarizes status of field: great progress on drugs (3 available), EMCF-sponsored contributions to field diagnostics, and a vaccine promising (with molecular biology advances) but not imminent.
- 1984: (July) First trachoma grant made.
- 1984: (November) President Reagan re-elected.
- 1984: Workshop on trachoma to develop strategic plan.
- 1985: (January) First grant made for oncho research.
- 1985: (February) President Coleman announces he will leave in mid-89.
- 1985: (April) Grant to survey pharmaceutical companies with operations in Brazil and Egypt to determine if any have capacity for schisto vaccine production.
- 1985: (April) Grant awarded to produce Oncho Update, quarterly bibliography of oncho papers, beginning with 1984 references.
- 1985: (September) Strategic plans for oncho and trachoma distributed to Board.
- 1985: (October) Goffman's final report: Ten years of Schisto Funding."

APPENDIX B
(continued)
Narrative Timeline Of Important Events

- 1985: New Initiatives sub-program. Ideas included International Health Consultative Group, leadership development, fund for health technology in developing world.
- 1986: (February) Oncho molecular biology conference sponsored by EMCF.
- 1986: (April) Peter Bell becomes EMCF President.
- 1986: Trachoma workshop advisors suggest investigation of surgical techniques.
- 1986: (April) Grant proposal introduced to Board to support International Development Research Centre (IDRC), Canada, to do study of developing country health needs. Proposal deferred after Board discussion concerning fit with TDR mission.
- 1986: (September) Workshop to initiate and foster trachoma epidemiology research.
- 1986: (September) Launching of the IDRC's Independent International Commission (IIC) to examine health needs of developing world. Later known as Commission on Health Research for Development.
- 1986: Statistics on worldwide tropical disease research funding: \$100M in US; WHO/TDR average annual budget since 1975 still \$20-25M.
- 1986: Howard Hughes Medical Institute grantmaking program established, Perpich at reins. EMCF organizes Schisto Task Force.
- 1987: (June) Dr. Cook anticipates that further support to labs working on schisto vaccine would be in form of coordination rather than direct lab support.
- 1987: (July) Planning meeting for IIC in Switzerland; funded by UNDP, Rockefeller, and Swiss Development Agency. Participation by many US-based international health funders, several European bilateral aid agencies, Bank, UNDP and WHO.
- 1987: Phase IV trials for ivermectin proceed; Merck announces Mectizan[®] Donation Program in October.
- 1988: (September) Grant for surgical treatment of trichiasis clinical trial. EMC makes self-grant to coordinate preparation, prosecution and maintenance of patent applications for inventions conceived of during the course of EMC support for TDR Program. Board approves IDRC grant.
- 1988: (November) George. Bush elected U.S. President. Trachoma grading scheme developed; grant to WHO to develop 12-country training program.

APPENDIX B
(continued)
Narrative Timeline Of Important Events

- 1988: (December) American Society of Tropical Medicine urges U.S. to increase funding for tropical diseases.
- 1989: Task Force for Disease Eradication formed in April at Carter Center. Targets polio, guinea worm, yaws, measles and rabies. Dana Foundation early contributor.
- 1989: Dr. Cook proposes five more years of schisto funding at 900K/year due to promising results in vaccine development.
- 1990: Question raised regarding further support for recombinant antigen approach to schisto vaccine development.
- 1990: (May) Commission on Health Research for Development releases report in May promoting broad vision of the interdependence of health and development.
- 1990: (December) Mr. Bell named Chairman of Board at CARE. (Bell remained at Clark Foundation until 1995, when named President of CARE.).
- 1991: (March) WHO to assume responsibility from Vanderbilt for Schisto Task Force.
- 1991: (May) Board discusses when/how programs should change direction. Concludes Board decides when direction should change, based on advice from program director and his/her advisors.
- 1991: (September) Oncho Task force to move from U. Alabama to FAES, with PI's move to NIH.
- 1991: Task Force for Child Survival plans a National Expanded Program in Chemotherapy in Ghana. Will focus first on schisto then oncho and helminths. EMCF starts to focus on "capacity-building" as follow-on to ENHR report.
- 1992: Partnership for Child Development (PCD). Research findings from EMC projects have contributed to organization of PCD—*"a loose confederation of agencies and foundations interested in improving health in the developing world by fostering programs for control of helminths and micronutrient supplementation."* School-aged children Program concept introduced to Board.
- 1992: (September) Helen Keller International (HKI) to assume the administrative responsibility for Trachoma Task Force and to assist WHO in developing national control programs.

APPENDIX B
(continued)
Narrative Timeline Of Important Events

- 1992: (November) Bill Clinton elected US President. Domestic health policy reform key agenda item.
- 1992: (December) Report to Board recounts disappointment of WHO/TDR schisto grant; questions whether to continue funding to WHO for role in Task Force.
- 1992: Pfizer's Zithromax® approved by FDA.
- 1993: Dr. Michael Reich reports on policy formulation in Ghanaian program (decision mapping). First mention of Pfizer emulating Merck with Zithromax®. WB's World Development Report: Investing in Health published. Burden of disease measurement "DALY" introduced. Report prompts further discussion of new directions for TDR. First HSAC grant.
- 1993: (March) Under new NIH guidelines, FAES will no longer administer external support for NIH intramural scientists' research.
- 1993: (March) Grant to HKI to coordinate activities in preparation for multi-center ("ACT") trial of Zithromax® for trachoma.
- 1993: (September) Final grants for trachoma vaccine research. Staff expects to wind down trachoma funding in 1995.
- 1993: (December) Initiating independent review of Oncho Program to decide on whether to curtail work on oncho vaccine.
- 1994: (March) Seven commissioned papers re new directions reviewed. Health-of School-Age Children opted for exploration. Grant to WHO to produce and disseminate technical training materials on control of trachoma.
- 1994: Oncho review workshop. Staff, thereafter, recommends shifting EMCF role from direct research to support of research resources.
- 1995: Mr. Bell announces departure to CARE; Dr Lawrence departs Rockefeller for JHU. APOC established.
- 1995: (March) Grant to Harvard to build on school-age children findings, and facilitate consultative meetings on health of school-age children in Sub-Saharan Africa.
- 1995: (April) Board retreat to examine what EMCF programs have tried to achieve, how they have gone about it, what they have achieved, and whether and how the foundation might go about its work differently in the future.

APPENDIX B
(continued)
Narrative Timeline Of Important Events

- 1996: (February) Michael Bailin succeeds Peter Bell as EMCF President. Capacity building through public health now on table. TDR working with Ghanaian SPH. Pfizer commits to the Moroccan national trachoma elimination plan. First hints of Program closeout for TDR as whole. GET2020 Alliance formed.
- 1996: (June). Mr. Bailin proposes that Board address planned revision of TDR strategy, shifting from school age children to public health training and institutional capacity building. SAFE strategy, validated over the years, provides opportunity to institutionalize trachoma control. This might be alternative to capacity-building strategy in Ghana and Tanzania, or both might be pursued.
- 1996: (September) Mr. Bailin highlights opportunity to reinvest in trachoma, building on Foundation's successful meeting on trachoma control and Pfizer's interest in donating the drug in Morocco.
- 1996: (November) U.S. President Bill Clinton re-elected.
- 1997: Staff cancels final cycle for vaccine development proposals, and decides no further oncho grants would be recommended.
- 1997: (March) Joe Cook, Mike Bailin, Ed Schmults, Larry Clark meet with control experts and Pfizer representatives regarding trachoma control using SAFE, including Zithromax®. Dr. Cook indicates to Board that Public Health capacity-building a long-term approach, and EMCF should instead pursue trachoma control opportunity.
- 1997: (May) Final AC meeting for TDR. AC to be reconvened with trachoma experts.
- 1997: (June) Grant to Harvard to assess criteria for selecting trachoma control participation countries.
- 1997: (August) Board retreat, President Bailin talks about institutional-and field-building, tying the exit of a program *"to the creation of some lasting institutional strength that the field has previously lacked."*
- 1997: (December) Grant made to support planing of a trachoma control initiative in Tanzania, in collaboration with Pfizer, should they expand their donation program beyond Morocco.
- 1998: (March) President Bailin plans "stocktaking" and "life cycle" discussion with Board, along with institution-and field-building, and advisory committee roles in future.

APPENDIX B

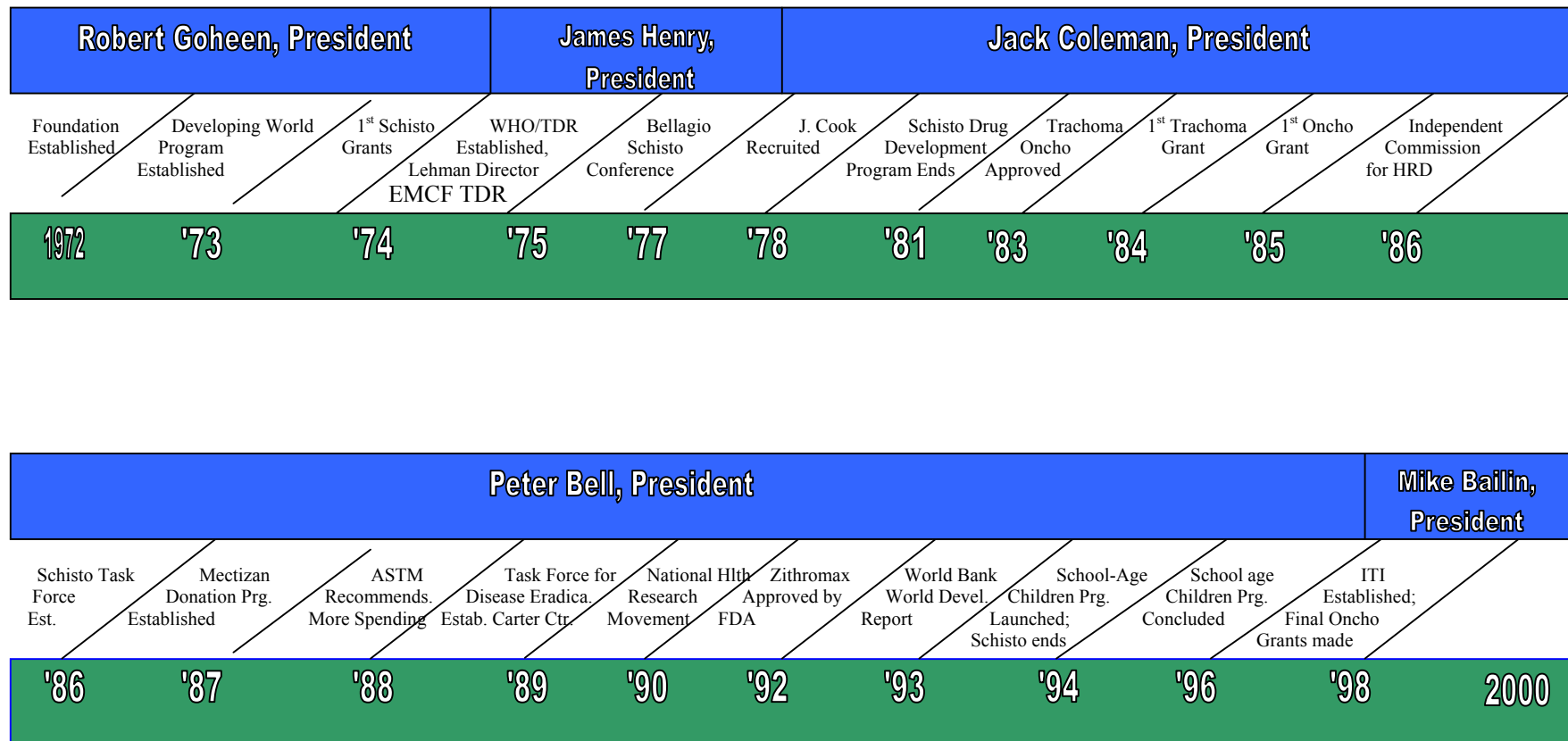
(continued)

Narrative Timeline Of Important Events

- 1998: (June) Board approves plans for up to \$4M grant to HKI for the International Trachoma Initiative with Pfizer, with all ITI activities transferred from EMCF to HKI by June 1999. Board agrees to leave to Mr. Bailin, in consultation with Board member Ed Schmults, all decisions concerning ITI's staffing, Board appointments, and processes.
- 1998: (September) Negotiations completed with Pfizer, and Board approves \$3.2M for HKI for the ITI, an example of field-building that creates an intermediary organization, ending EMCF's direct involvement in trachoma.
- 1999: (January) ITI Board representatives from EMCF are Mr. Bailin, and Board members Ed Schmults and Larry Clark.
- 1999: (May) Dr. Cook provides presentation to Board on ITI progress. Dr. Hunter, assessment director, and Mr Bailin describe three projects to extract lessons learned from TDR. Support for on-going efforts concerning capacity-building in Ghana and Tanzania, and for oncho vaccine development will end at the end of 1999.
- 1999: (September) Board dinner to celebrate accomplishments of the TDR Program, and Dr. Cook's leadership. Dr. Cook provides Trachoma Program Update Strategy and indicates that he is hopeful that continued progress over the next year will provide reason for EMC to sustain support for ITI beyond September 2000.

APPENDIX C

Edna McConnell Clark Foundation Tropical Disease Research Program: Important Events 1972-2000



APPENDIX D
GRANT HISTORY 1974-1999

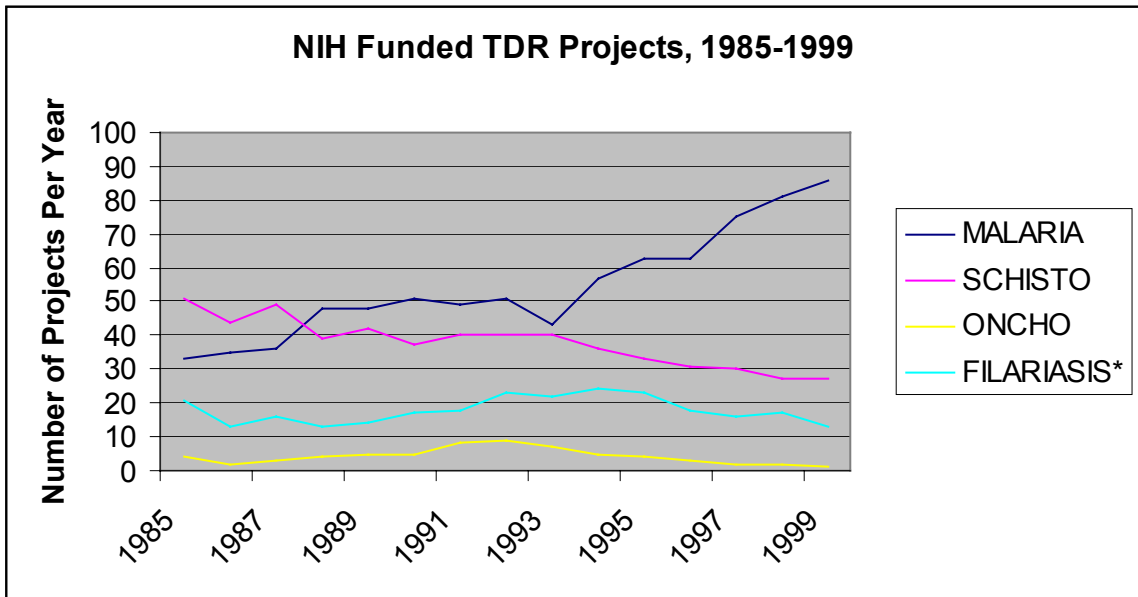
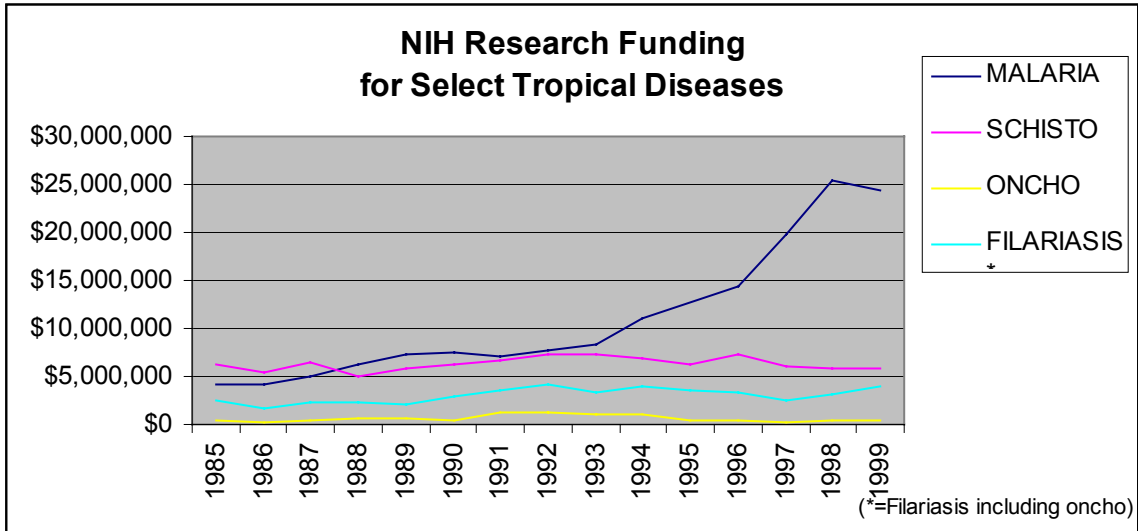
Program	Grant Count	Grant Amount	Average Grant
Schistosomiasis			
Immunology and Vaccine Development	134	16,546,012	123,477
Biochemistry and Drug Development	71	5,715,981	80,506
Epidemiology and Disease Control	127	10,122,530	79,704
<i>Subtotal: Schistosomiasis</i>	<i>332</i>	<i>\$ 32,384,523</i>	<i>\$ 97,543</i>
Onchocerciasis			
Immunology and Vaccine Development			
Animal Models	17	3,053,000	179,588
Antigen Identification	67	11,031,679	164,651
Antigen Screening	6	726,000	121,000
Immune Mechanisms	10	1,108,792	110,879
Research Resources	30	4,578,732	152,624
Other I&V	3	128,000	42,666
Oncho Other			
Task Force Support	6	819,500	136,583
Communications	3	74,535	24,845
Field Research	2	75,000	37,500
<i>Subtotal: Onchocerciasis</i>	<i>144</i>	<i>\$ 21,595,238</i>	<i>\$ 149,966</i>
Trachoma			
Immunology and Vaccine Development			
Animal Models	9	1,718,986	190,998
Antigen Identification	20	3,816,244	190,812
Immune Mechanisms	15	2,386,132	159,075
Pathogenesis	10	1,638,000	163,800
Epidemiology and Control	43	8,744,408	203,358
Operational Research	18	1,678,000	93,222
Capacity Building	10	1,602,500	160,250
Coordinating Entity	9	3,911,500	434,611
Communications	8	645,000	80,625
Country Programs	8	1,874,000	234,250
Other/Unspecified	1	145,000	145,000
<i>Subtotal: Trachoma</i>	<i>151</i>	<i>28,159,770</i>	<i>186,488</i>

APPENDIX D
(continued)
GRANT HISTORY 1974-1999

Program	Grant Count	Grant Amount	Average Grant
Health of School Age Children			
Ghana			
Capacity Building	1	200,000	200,000
Research	3	630,000	210,000
Other	1	430,000	430,000
Tanzania			
Capacity Building	2	680,000	340,000
Research	2	400,000	200,000
International			
Capacity Building/ Technical Assistance	7	1,227,000	175,285
Other	3	258,000	86,000
Other/Unspecified	4	485,000	121,250
<i>Subtotal: HSAC</i>	<i>23</i>	<i>4,310,000</i>	<i>187,391</i>
“Other”			
Exploratory	20	1,552,062	77,603
Prevention of Blindness	4	135,000	33,750
Other	17	1,834,845	107,932
<i>Subtotal: “Other”</i>	<i>41</i>	<i>3,521,907</i>	<i>85,900</i>
Totals	691	89,971,439	130,204

APPENDIX E

NIH Tropical Disease Research Funding, 1985-1999 Malaria, Schisto, Oncho, Filariasis*



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