CHAPTER 1

The Intellectual Origins of the Children's Vaccine Initiative

The organization called the Children's Vaccine Initiative (CVI), founded in 1990–91, was designed to revolutionize the development of vaccines for the Third World. Its goals were nothing less than to create a mechanism for "overseeing the whole [vaccine] process, from conception . . . at the laboratory bench to its development by industry and its incorporation into vaccine programmes."[1] The vital "product development" part of the process, which is often overshadowed by the more glamorous "breakthroughs" of laboratory research, was of especial concern. It "is the costly and time-consuming effort that includes producing small but high-quality batches of a candidate vaccine for testing, running clinical trials to demonstrate safety and effectiveness . . . determin[ing] appropriate doses, [and] meeting licensing requirements,"[2] and then goes on to include full-scale manufacturing, packaging, shipping, and advertising of the resulting product. Most potential vaccines are lost because no one is willing to bring them through this process to fruition.[3] The fact that the process is estimated to cost anywhere from $50 to $200 million is the reason.

The CVI was created as a response to the disarticulation that characterized vaccine development on the international level. The fragmentation of the "system" manifested itself at a number of strategic points. First, individuals and groups concerned with conducting the basic laboratory research necessary to create protovaccines knew little about the elaborate and costly product development process outlined above. They usually did their research without communication with potential developers, and as a result the shelves of research facilities were filled with vaccines that had reached the "proof of principle" stage but were not picked up by those who make usable commodities.

Second, those groups that carry out the job of delivering childhood vaccines to the developing world have little interaction with either the scientists conducting basic research, or the commercial interests that decide which vaccine candidates are worth bringing to full-scale production. While basic research is largely "investigator-initiated" (i.e., propelled by the individual interests of the scientists), actual product development is driven by the needs of companies to obtain a commer-

cial profit. Those who deliver vaccines to the children in the developing world are forced to use whatever vaccines the other two groups have decided, for their institutional or individual reasons, to work on—with little positive input from the deliverers in the field. Such a threefold division of responsibility and expertise, with limited communication between the three groups, has made it impossible to maximize the power of science to protect the lives of children in the developing world.

In addition, the problem is compounded by the fact that the public sector, while intensively involved in funding basic research and paying for vaccine delivery, has not been well represented in the indispensable middle stage—product development. This has left a major gap in public involvement, which exacerbates the already destructive lack of coordination between the three areas. The initial impetus behind the founding of the Children's Vaccine Initiative was less the need to coordinate the three-part system, as vital as that was, than it was to exert a greater public sector influence over the product-development stage of the process.

A REVOLUTION IN THE LABORATORY

The momentum that ultimately led to the formation of the new organization started to build in the late 1970s as a result of the biotechnology revolution in basic research—an upsurge of new knowledge and techniques that promised to radically transform the nature of vaccine product development. The situation was well summarized by Dr. Kenneth Warren, director of health sciences of the Rockefeller Foundation, in his testimony before the House Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce (i.e., the Dingell committee):

> The vaccines of the past have either been found by accident, by luck, or by good observation and have been largely crude mixtures of whole organisms. . . . [B]iotechnology enables us to: . . . identify the precise materials necessary to protect us against infectious agents; . . . produce them in bacterial factories in large quantities; . . . analyze their chemical structure; . . . break them down into smaller fragments which may retain their protective role; and . . . produce the synthetic vaccines chemically. Furthermore, we can use living bacteria and viruses to insert the genetic material from several different organisms simultaneously into the host, which will then produce its own vaccines.[4]

THE AMERICAN EFFORT

The new scientific potential created great excitement among researchers throughout the world. The first group to try to harness the new tech-

nology was the (U.S.) National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). NIAID was the driving engine for vaccine research in the United States. In 1981 they created the "Program for the Accelerated Development of Vaccines."[5]

NIAID led the way because the new molecular biology and recombinant DNA techniques that constituted the biotechnology revolution had resulted from programs supported by the Congress and the National Institutes of Health. NIAID had quickly assembled the personnel and equipment necessary to utilize the discoveries. As a result of "discussions and ferment" in 1978–79 the Accelerated Development Program was created. The program envisioned a broadly cooperative venture involving many of the Public Health Service agencies that dealt with vaccine development, including several of the institutes of the NIH, the Food and Drug Administration (FDA), and the Centers for Disease Control (CDC).[6] The initial plan called for the creation of a formal interagency work group composed of members possessing strong contacts with academic and international circles, and ties to both government and industry.[7] The cooperation of the different agencies was seen as indispensable for an effective accelerated program.

In fact, the ambitious new program was never funded. While it looked impressive on paper, it came up against the major cutbacks of federal agencies initiated by the Reagan administration in the early 1980s. Intensive questioning by members of the Dingell committee forced Dr. James Mason, assistant secretary for health, and Dr. William Jordan Jr., director of the Microbiology and Infectious Disease Program, NIAID, to admit that the acceleration program was little more than a pious wish.

In the absence of new funding, the leadership of NIAID was forced to support the idea of speeded-up vaccine research by shifting money in-house from other projects toward designated high-priority vaccines. Such a process left the individual projects very thinly covered. As Kenneth Sell, M.D., former scientific director at NIAID, put it to the committee, the NIAID "covered all bases" but often had only one grant or a small number of scientists working on any particular vaccine—which did not constitute much "acceleration."

In addition, under the pressure of the AIDS crisis, money was shifted away from such vital vaccines as pertussis, hepatitis, and rotavirus toward AIDS research. The Dingell committee pointedly contrasted the reality of vital vaccines languishing for lack of funds with the government's vociferous insistence that research for such necessities as a safer pertussis vaccine were on the "fast-track"—leaving assistant secretary Mason's protestations to the contrary sounding hollow, if not mendacious.

Kenneth Warren, in his testimony, told the committee: "When you talk to scientists in this field [generally,] many will tell you that they are bootlegging [vaccine research] on their other grants. They don't have specific grants for doing vaccine work."[8] The veracity of this position was supported by what was happening at NIAID.

Despite the lack of substance to the accelerated vaccine program, its existence, even if primarily on paper, had a momentous side effect that intensified interest in vaccine development both in the United States and overseas. As part of the official commitment to speeding vaccine research, the staff of NIAID's Microbiology and Infectious Diseases Program had a three-day meeting in the fall of 1980 in which they reviewed the status of approximately thirty diseases. At that meeting they composed a tentative list of vaccine priorities. In 1981, they contracted with the Institute of Medicine (IOM) of the National Academy of Science to create a more definitive ordering of vaccines for development.

The Institute of Medicine produced two landmark studies that assessed which potential vaccines could be developed in the near future and then it proceeded to prioritized them on the basis of a series of flexible but reproducible criteria. The first volume dealt with vaccines needed in the United States, while the second emphasized diseases in the developing world. (Interestingly enough, the resulting list of vaccines for the Third World was very similar to that which the NIAID staff had generated on its own in 1980.)[9]

The IOM studies maintained that there were nineteen vaccines that could be quickly developed for the Third World, and an additional twelve for the United States. Their findings constituted a direct challenge to scientists and policymakers throughout the world to use the new biotechnology to save lives.[10] While the questioning of assistant secretary Mason by the Dingell committee made it clear that the Reagan administration had no intention of funding the IOM recommendations, and in fact had put vaccine development "on a backburner," the very existence of the studies strengthened the belief among scientists that great achievements in the field of vaccines were both possible and morally imperative. Thus, despite the funding problems that dogged researchers, the scientists at NIAID and those consulted by the Institute of Medicine, were clearly excited and hopeful about the future of vaccines—as were their peers worldwide.

THE BELLAGIO CONFERENCES

Sir Gustave Nossal, a world-renowned immunologist from Australia, took the issue of the biotechnology revolution to center stage at an inter-

national gathering of health leaders meeting in Bellagio, Italy, in March 1984. The landmark Bellagio Conference—sponsored by the Rockefeller Foundation—brought together the heads of WHO, UNICEF, the World Bank, the United Nations Development Programme (UNDP), the Rockefeller Foundation, and many of the most important bilateral donor agencies. The meeting was setup as an attempt to radically energize and transform the existing international vaccine programs—especially the World Health Organization's Expanded Programme on Immunization (EPI)—that were committed to immunizing the world's children. One major result of that meeting was the formation of the Task Force for Child Survival (TFCS), which provided an ongoing forum where the leaders of international health could come together and talk about ways of accelerating immunization activities.[11] The task force was designed to help overcome the institutional rivalries that plagued the United Nations agencies (UNICEF, WHO, UNDP, and the World Bank), especially in the area of health, which was technically the exclusive mandate of the World Health Organization—but whose ability to live up to its charge was widely questioned.[12]

Nossal's presentation, "The Biotechnology Revolution and New Vaccines," emphasized the immense opportunity that basic research now offered the world in its fight against disease. He told them of

> the excitement which is sweeping through academia. . . . [Since d]reams of great daring are being dreamt, extending the concept of vaccination from viruses and bacteria to single-celled or multicellular parasites and even to non-infectious diseases like cancer and multiple sclerosis. . . . The sky seems to be the limit.[13]

He argued that concentrating on delivering health services and current vaccines (i.e., the current EPI) without putting money into basic research and clinical trials to develop a usable product was folly. He challenged the meeting to support the new biotechnology by "influenc[ing] world opinion concerning the design and implementation of clinical trials . . . and speeding the movement from laboratory research to . . . forceful clinical research."[14] Nossal told them that new vaccines were stalled "in the wings" because of inadequate "financing and moral backing" and what was needed was simply to drop "a crystal in the supersaturated solution" created by the scientific excitement and the revolutionary potentialities. He clearly hoped that the Bellagio Conference would provide that "crystal."[15]

Nossal's argument for the importance of scientific breakthroughs was repeated in the following year at Bellagio II, under the auspices of the Task Force on Child Survival, which was held at Cartegena, Columbia, in October 1985. Dr. D. A. Henderson, the man who directed the suc-

cessful WHO program to eradicate smallpox, warned his audience that delivering vaccines effectively could not be separated from basic research. He complained that "a number of persons, some of whom ha[ve] important roles, have suggested that the problem [of vaccines] is simply one of mobilizing political will and administering vaccines of proven efficacy." That benighted position, he said, was raised in the campaign against malaria—in which skilled "malariologists" rather than the disease were "eradicated"—and again during the smallpox program where "reputable scientists and health officials alike challenged the need for research." He pointed out that the successful war against smallpox could not have been won without research and that "not one of the six vaccines [i.e., polio, tuberculosis, diphtheria, pertussis, tetanus, measles] we are using in the [EPI vaccine delivery] program is fully satisfactory" or even up to the level of smallpox vaccine.[16]

Kenneth Warren also championed the importance of basic research, as opposed to an exclusive emphasize on the problems of vaccine delivery. He, clearly influenced by Nossal's talk the year before, spoke forcefully of "the pressure . . . building up, . . . [so that] it is now inevitable that there will be a virtual eruption of vaccines within the next 15 years." However, he was not blind to the mindset that stood in the way of utilizing the new opportunities,

> [w]hen three well-informed individuals, a trustee of the Rockefeller Foundation, a member of the World Health Assembly of the World Health Organization, and a director of UNICEF say, "Why should we develop new vaccines when we haven't applied those now available?"

The answer, said Warren, was that biotechnology would provide solutions to the existing practical problems that made it extremely difficult to use current vaccines: the need for an expensive "cold chain" (to keep vaccines cool in tropical climates), the requirement for multiple shots, toxic side effects, and poor administration.[17]

THE PROGRAMME FOR VACCINE DEVELOPMENT

Warren's dedication to furthering biotechnology and vaccine development was not restricted to his attempt to persuade the policymakers assembled at Bellalgio II of their importance. He had already helped bring to fruition what he hoped would be a decisive advance in the public sector's involvement in these areas: the creation in 1984 of the Programme for Vaccine Development (PVD) as a special program of the World Health Organization.

The immediate origin of the PVD came from discussions between Warren and Dr. Fakhry Assaad, WHO's director of the Division of

Communicable Diseases. Together they came up with the idea of starting a program that would encourage vaccine research and product development.[18]

Soon after these discussions, Warren was contacted by the head of Health Programs at the Pew Charitable Trusts, one of the largest American foundations, and informed that Pew wished to sponsor an international project but was not sure where to place its money. After discussions between the two foundations, they proceeded to provided the necessary seed money ($4 million) to launch the PVD.

While Warren considered Assaad one of the most qualified people in the world of international health, he had strong doubts about the general abilities of the staff at the World Health Organization in Geneva. One of Warren's basic objections to the agency was its commitment to distributing jobs by country—a procedure that he felt usually guaranteed mediocrity. He made sure that the new PVD would hire and contract work only on the basis of scientific merit and thus be exempt from the normal WHO system.[19]

The PVD was an early attempt to create a Children's Vaccine Initiative–type structure that would utilize the advances being generated by biotechnology and work to overcome the lack of coordination in vaccine research. This foreshadowing was even stronger after the addition in 1987 of a new component of the PVD called Transdisease Vaccinology that tried to solved general problems of vaccine effectiveness that could impact a wide range of diseases.[20] By 1990 the PVD would have 87 projects in 19 countries that dealt with such problems as:

> Development of live viral or bacterial carriers for multiple vaccine antigens. Development of vaccines for intranasal or oral administration. Improvement of vaccines stability. Development . . . of [better vaccine] adjuvants. Control release vaccines, i.e., antigens in micro-capsules, formulated as a one shot vaccines, [that are] . . . programmed for continuous release over a prolonged period.[21]

But as we will see later, despite the PVD's scope, it did not live up to Warren's expectations.

THE IDEAL OF A PERFECT VACCINE

Warren in part credits his effort to set up the PVD to the inspiration he received from Dr. William Foege, chairman of the Task Force for Child Survival, on the importance of "applied research" for vaccines. A clear statement of Foege's views was presented by him in his presentation at Bellagio II in Cartegena in 1985. Many, including Warren, consider that presentation the intellectual inspiration for the Children's Vaccine Initiative.

While the PVD was an early attempt to operationalize some of Foege's ideas in the mid-1980s, their real fruition would only come in 1990.[22]

Where Warren, Nossal, and D. A. Henderson in their Bellagio presentations emphasized the importance of basic scientific research for the creation of new vaccines, Foege staked out as his ground (and that of the Task Force for Child Survival), the area of "applied" or "operational" research. He felt that basic scientific research was being dealt with by a number of groups, especially the World Health Organization with its newly formed PVD, and the Scientific Advisory Group of Experts (SAGE), which gave guidance to the PVD. Such research did not need a new task force study to go forward. However, no one was systematically looking at applied research and its role in furthering immunization.[23]

Foege knew what the problems in applied research were because the task force had "put out a request to the . . . [program managers] in the field asking what needs to be done in order to improve life for you. . . . If you could solve any problem what would it be?"[24] One of the major findings of that inquiry was that if program managers had the power to design an ideal vaccine, "[t]hey would develop a multi-antigen vaccine (that is, containing all antigens in a single injection), that would":

1. Provide lifelong immunity with a single dose;
2. Have no short-term or long-term adverse reactions;
3. Be inexpensive;
4. Be easily administered without costly equipment or techniques by relatively untrained workers;
5. Be stable at tropical temperatures for months, or even years;
6. Be efficacious any time after birth.

Foege was optimistic that many of those attributes could be achieved before the turn of the century.[25] The "ideal" vaccine that Foege believed the program managers desired would ultimately be christened, five years later, "The Children's Vaccine."

In his Cartegena presentation, Foege juxtapositioned the areas of basic and applied research as competing areas of interest and investment. He pointed out that "Applied research, while suffering from a lack of glamour in the past, will have an even harder time in the future . . . [as t]he excitement of basic biomedical research increases . . . [and] the competition for resources becomes even more skewed."[26] He was certainly correct that there was a strong tendency for basic researchers to ignore applied research (and vaccine development as well). Indeed, Warren's high hopes for the Programme for Vaccine Development would be sorely disappointed after the premature death of

Fakkhry Assaad, as its leaders increasingly emphasized basic research at the expense of product development.

Nevertheless, as useful as Foege's comparison between applied and basic research was in creating an intellectual space for field-oriented problems, the division between basic and applied research in practice was easy to exaggerate. The "ideal vaccine" that Foege talked about could only be developed by constant communication and feedback between applied and basic researchers. Each characteristic of the ideal vaccine that field managers demanded raised problems that only more basic science could resolve. While basic researchers unfortunately could, and did, ignore applied researchers, the opposite was not possible. For applied research to be effective, the conceptual wall between the two areas had to be continuously breached. A more useful way to look at the differences between types of research is between "applied and not yet applied research."[27]

(In the same vein, "product development" and "basic research" are often seen as competing areas of work. However, effective development often requires continuous interaction with basic scientists to answer unexpected problems as they arise. The Children's Vaccine Initiative would initially see itself as a champion of product development rather than basic research, only to discover that key scientific questions remained unanswered, and development could not go forward without the help of additional focused basic research.)

THERE ARE RISKS AS WELL AS OPPORTUNITIES IN THE VACCINE REVOLUTION

Between Foege, Warren, Nossal, and D. A. Henderson, as they expressed themselves in 1984–85, the intellectual seeds of the CVI were planted among the major policymakers in the international health community; and such seeds already existed among scores of working scientists in government and academia. Their message was one of excitement and hope. Nevertheless, their extreme optimism was tempered by the recognition that counterforces existed that threatened to nullify the new opportunities. As we have already seen, in 1985 both Foege and Warren testified before the Dingell committee. Their appearance in Washington was engineered by two staff members of that committee—Anthony Robbins, M.D. (ex-director of the National Institute of Occupational Safety and Health) and his wife Dr. Phyllis Freeman, J.D. They were very concerned about the effects of the conservative Reagan administration, and its Office of Management and Budget, on the funding of vaccine research and development.

In the years after 1985 Robbins and Freeman became powerful spokespeople, at conferences, in government, and in print, for the proposition that the movement toward conservative government, combined with the rapid privatization and consolidation of the vaccine industry, threatened to make it impossible to produce affordable vaccines for the developing world regardless of the new biotechnology. The 1980s, they said, was a period of immense dangers as well as opportunities.

Vaccine production, Robbins and Freeman pointed out, had traditionally been a public sector function but over the years many of the public institutes that produced vaccines stopped functioning or were absorbed by for-profit pharmaceutical companies. Increasingly vaccines were coming to be seen as just another form of commercial merchandise that had to produce a profit rather than a special kind of "commodity" designed for the public. Robbins and Freeman became major proponents of a more aggressive public sector role in vaccine product development. They felt it was an area too important to leave to private enterprise alone.[28]

BEGINNING-TO-END VACCINE DEVELOPMENT

Robbins and Freeman, as key staffers for Rep. John Dingell and the committee he headed, had to familiarize themselves with the vaccine situation internationally as well as in the United States. They had a great deal of interaction with the dominant figures in both science and policymaking. They were very aware of the powerful ferment among scientists that Nossal and the others were talking about. Phyllis Freeman, especially, was taken aside by those most knowledgeable about vaccines and "educated" as to where the problems in the field lay. Especially important was the influence of Philip Russell, M.D., commanding general of the U.S. Army Medical Research and Development Command. General Russell was one of the few scientists in the world with in-depth experience with the vaccine product development process from beginning to end. The U.S. Army was deeply involved with the development of new vaccines because of the problems raised whenever large numbers of immunologically immature recruits were brought together in military camps, and the dangers posed when American troops were sent overseas. The Army, unlike the public sector generally, worked closely with private pharmaceutical companies to make sure that the vaccines it need were actually produced. It could not afford to leave decisions to the marketplace.

Freeman and Robbins' realization that as bad as the vaccine situation was in the United States it was worse in the developing world, led

them both to become involved with the Task Force for Child Survival—where Robbins would become the director of the Vaccine Development/Production Initiative. In that capacity Robbins promoted the idea of a research incentive system known as "front-end" funding. Under that approach "financial assistance for vaccine development [would be offered] to commercial manufacturers and public health institutes as a means of offsetting high research costs, in exchange for lower vaccine prices."[29] The task force adopted this policy and actively solicited proposals.

Robbins would also work closely with both Scott Halstead of the Rockefeller Foundation and Frank Hartvelt of the United Nations Development Programme (both members of the Task Force for Child Survival) in their attempt to alert the World Health Organization that "Everyone has recognized the need to confront the advanced development and production steps that separate the PVD [of WHO] from actual use of a new or improved vaccine in EPI"—the yawning gap that Phil Russell had long argued against.[30]

Gustave Nossal, at Bellagio I, had said that what was need to revolutionize the fight against disease was simply "a crystal in the supersaturated solution" that was created by the scientific excitement over the potential of biotechnology. That precipitant was not provided by the Bellagio Conference nor even the Task Force for Child Survival that it spawned. The solution would not actually be saturated enough until the interconnected arguments of people like Nossal, Foege, D. A. Henderson, Russell, Warren, Robbins, and Freeman were fully digested by health policymakers and scientists.

D. A. HENDERSON AND THE PROBLEM OF POLIO ERADICATION

The chain of events that directly lead to the founding of the Children's Vaccine Initiative were set in motion, inadvertently, by Dr. Ciro de Quadros, senior immunization advisor to the Pan American Health Organization (PAHO), at Bellagio III, in Talloire, France, in March 1988. At that conference de Quadros reported on the efforts of PAHO to eradicate polio in the Americas. He then called on the policymakers present at the conference to endorse a call for the global eradication of the disease.[31] Ultimately, the conference did endorse the idea of polio eradication—and it was later adopted by the World Health Assembly of WHO as an official goal.

However, D. A. Henderson, the director of the earlier smallpox eradication program and rapporteur for Bellagio III, was less than

enthusiastic with the proposal. Despite the fact that Henderson has the reputation of being a disease "eradicator," and has been assumed to be the leader of a "triumvirate" (composed of himself, Drs. Ciro de Quadros of PAHO and Isao Arita of the Agency for Cooperation in International Health [ACIH] of Japan), dedicated to pushing polio eradication at all cost, he has always had strong reservations about such a goal:

> I am not a bold eradicator. Every time you turn around someone suggests another disease to eradicate. I flinch. I know how hard it was to eradicate smallpox. There are several bandwagons a year. . . . The Malaria Eradication Program of 1955 . . . was based on very poor science, [it was] irrational . . . [and] got hopes up all over. . . . The credibility of the pubic health community was jeopardized.[32]

He believes regional or global eradication campaigns can under certain circumstances be very useful—but not solely because they eliminate a specific disease. Their true usefulness lies elsewhere. If you went to a government and

> try to sell basic health services it is as un-sexy as you can get. . . . If you argue the case of polio eradication . . . you get the interest of heads of states far easier than if you say you need better immunization programs . . . [with that] you get a big yawn.[33]

The men who make investment decisions for governments, he says, are usually not medical people but economists and politicians, and for them eradication has a beginning and end; it produces a "final" product. Thus, you can use an eradication campaign as an opening wedge for more fundamental health work. For example, in the Americas it became clear that the

> polio program was going to be the cutting edge, and you could bring in the rest of the program that is less sexy. You could build surveillance systems for polio and use it to strengthen immunization activities . . . in [the] Americas . . . [the system] also reports measles and tetanus as well as polio.[34]

To Henderson the construction of a sustainable infrastructure for disease surveillance was vital, and it was not getting the attention from international and national health agencies that it deserved.

The problem for Henderson in expanding the polio eradication program from the Americas into a global campaign was that he did not consider the existing vaccine good enough. It was less potent and stable in tropical areas than in the developed world where it had been created. Thus, it was an error to start a campaign "without simultaneously committing to improve the vaccine."[35] As a result of his position (he was

chairman of the Technical Advisory Group advising PAHO on the polio campaign) and his great prestige in the health community, the sponsors of the polio eradication proposal gave him their assurance that they would fund the necessary research to improve the vaccine:

> As you know, I [Henderson] chose not to subscribe to the original paper advocating a global poliomyelitis eradication program [because] we did not have a sufficiently antigenic and heat stable vaccine. . . . At Talloires [the Bellagio III meeting], I was persuaded by you [Ralph Henderson and William Foege] and others to support a call for global . . . eradication . . . on the assumption that an intensive research effort would be launched.[36]

After the World Health Assembly in 1989 endorsed the goal of polio eradication, Henderson was dismayed to find that months went by and none of the agencies honored their commitment to support polio research. He was determined that the pledge not be allowed to die. As a means of raising the issue he wrote a letter to William Foege, the chairman of the Task Force for Child Survival—with copies to leaders of WHO, UNDP, and UNICEF. In that letter he put the issue of the polio vaccine into a much broader context of dissatisfaction:

> I have been concerned regarding the EPI [Expanded Programme for Vaccines, the major UN program for vaccination of children in the developing world] . . . and its future and that concern has been significantly heightened by [a] . . . report to me that the pathetically small amount of money available for WHO's vaccine research program [PVD] will be reduced by nearly a third with the conclusion of the Pew [Charitable Trusts] Grant. . . . [Both] EPI and polio eradication . . . [are] doomed if we don't have far better products in the field.[37]

D. A. HENDERSON MAKES A MOMENTOUS PROPOSAL

The dismaying information that Henderson alludes to above came from none other than Dr. Gordon Ada, an Australian, chairman of the Scientific Advisory Group of Experts (SAGE) that oversaw the PVD. Henderson and Ada proceeded to discuss the problem of vaccine improvement and development that plagued the world community. They agreed that the SAGE and PVD were oriented to basic research. Indeed, the SAGE had recently turned down an important research proposal for work on a heat-stable polio vaccine because it was "too applied." As a result of this, Henderson and Ada "felt a more broadly managed research and development program [was needed] rather than the PVD. . . . PVD was investigator-initiated [basic] research . . . but not hooked into people in the field that was needed [in order to direct them].

[This constituted] the gap [at WHO—between PVD and EPI]. [Henderson and Ada's managed R&D program] . . . would produce specific products"[38] and thus fill in the space that PVD and EPI left empty.

Where, Henderson wondered, could such a new program be put? The United Nations Development Programme lacked expertise in this area. UNICEF had no research component at all. The Rockefeller Foundation was very active in vaccine programs but there was "a strong suspicion of Americans and American domination of vaccines . . . [and] there was a lot of resentment [of the Rockefeller]. It would not succeed if it [the Rockefeller] was the home of the research enterprise."[39] In addition, Henderson and Ada were unsure how to launch such a broad research and development program. To make matters worse, D. A. Henderson did not find either Ralph Henderson of WHO or Foege of the Task Force for Child Survival supportive of such a broadly focused initiative. As a result, D. A. Henderson decided to narrow his focus down to the polio vaccine.[40] (Nevertheless, Henderson's later polio proposal and supporting correspondence all have strong echoes of his earlier, more broadly aimed research and development program.)

In September 1989, Henderson met with Ralph Henderson, Dr. M. Abdelmoumene (deputy director-general of the World Health Organization), and other WHO personnel in Geneva to discuss the polio vaccine. The group agreed there was a real need for a "imaginatively managed research effort":

> It is the consensus belief that the research effort should be under WHO auspices. How this might be done [however,] poses a quandary . . . [since t]echnical expertise is not now available in WHO and efforts to recruit suitable persons has proved to be all but impossible. The WHO Vaccine Development Program has proved useful in advancing the state of knowledge of vaccines in general . . . but is ill-suited to development when time constraints and highly targeted objectives dominate the agenda.[41]

Henderson and Ada, then a visiting professor at Johns Hopkins University, indicated their willingness to lead the effort but neither was prepared to move to Geneva to do so. They proposed as a possible solution a "WHO Polio Vaccine Center" based at Johns Hopkins University that could reach out to experts around the world.[42] The center would report on a regular basis to the EPI Research and Development Group "but would have a defined and reasonably broad latitude of discretion in decision-making, including decisions with regard to disbursement of funds."[43] (Such a level of autonomy constituted a remarkable delegation of power by WHO to an outside agent.)

After the meeting D. A. Henderson and Gordon Ada wrote up a

proposal that summarized the conclusions of that September meeting and titled it "A 'Manhattan-Type' Project for Improving the Stability and Efficacy of Polio Vaccine: Commentary and Proposal."[44] Copies of it were sent to the heads of the various agencies sponsoring polio eradication (WHO, UNDP, UNICEF, Rotary International) in order to inspire them to act.[45] Henderson followed up the mailing with personal visits to the leadership of the various organizations. The response to the (narrower) polio emphasis was instantaneous: Timothy Rothermel of UNDP gave $125,000 as immediate start-up money.[46]

D. A. HENDERSON APPROACHES UNICEF

On January 11, 1990 Henderson met with James Grant, executive director of UNICEF. If Henderson was going to do the work under WHO auspices, he would a need significant amount of money. WHO did not have the cash, but UNICEF did. Henderson told Grant that any private company as large as UNICEF would of necessity have a research and development component. How could UNICEF afford to ignore it? Polio was one of the six vaccines that UNICEF helped supply the countries of the developing world, and that vaccine desperately needed to be made more potent and heat-resistant if the eradication campaign was not to fail. To convince Grant that this should be of vital importance to him, he said, "Would the possibility of eliminating [an expensive] cold chain be of interest to you?" Most of the cost of delivering vaccines was not in the price of the material but rather in the cost of maintaining the cold chain that kept the vaccines cool under tropical conditions. If polio were heat-resistant, "then you can do away with the cold chain . . . [because the other] vaccines—measles, DPT etc.—are more heat resistant" than polio. If that argument was not enough to convince Grant, Henderson threw in another one: "Suppose instead of three doses [of DPT], what if one" dose would do. With microencapsulation even that might be possible. He challenged Grant: "Shouldn't UNICEF support it?" He also told Grant that there were studies being conducted on oral vaccines at that very moment and asked Grant, "Can you imagine one oral dose of DPT?"[47]

Henderson's verbal claims acted as a powerful reinforcement for statements he had already made in the written proposal that he had sent Grant in October 1989:

> Studies with a human fertility vaccine suggest . . . sustained release preparations might be able to be used with injectable inactivated vaccines. If the sustained released preparations proved effective . . . one can visualize a newborn infant . . . being fully immunized with a single

> dose of a sustained release preparation containing vaccines against polio, diphtheria, tetanus, pertussis, hepatitis B, haemophilus influenzae and perhaps others. Such a preparation would revolutionize not only the polio program but the entire immunization program.

Now, it is true that Henderson went on to write, "Unfortunately, work in this area has only just begun and considerable efforts would be needed" to make it work.[48] But it is not surprising that Grant, and later others, would be more inspired by Henderson's exciting vision of a revolutionary future than any cautionary notes he attached that qualified it.

(The irony here is that the scattered remnants of Henderson's original broad-focused research project that he left in his polio proposal and used to bolster his verbal arguments, should have triggered someone else to aim for the prize that Henderson initially sought. Ultimately, Jim Grant's vision would take a form that Henderson was less than happy with.)

Henderson's ideas, as we have seen, were not new; they had been presented at the Bellagio Conferences and the Task Force for Child Survival for a number of years, and Grant certainly had heard them.[49] But Henderson's presentation appears to have actualized the possibilities for Grant and inspired him to action in a way that had not been done before. Henderson believes that the concept of "The Children's Vaccine" was born in Grant's mind as a result of his interactions with Grant. As Henderson puts it: "His [Grant's] imagination took a leap—as it often did . . . a fantastic leap of faith."[50] However, as far as Henderson was concerned, the information he gave was only for "illustrative purposes," designed to inspire Grant to support polio research. As for Henderson himself, he

> never in a million years [would] propound such an idea. . . . [W]hat we did not need was a nirvana, a preposterous concept [of a single magic bullet] out there that was totally unreachable. We [Henderson and others] were afraid the idea of getting reasonable development research . . . [would be] torpedoed by this grandiose idea. . . . [T]o get money [for research] you needed a credible, scientific approach. . . . "The C[hildren's] V[accine]" was extreme.[51]

While Henderson's ideas provoked a greater response from Grant than was intended, it is probable that Henderson's actions (rather than words) also led to that same effect. What Henderson was trying to do in his "narrow-focused" polio project was little less than awe-inspiring. He was single-handedly attempting to revolutionize the way the international health community worked by creating a "Manhattan Project" that would

> set . . . in motion a collaborative program involving a diverse array of layers (i.e., research and development staff in academia, industry and government, field epidemiologists and multiple donors) who would contribute to the program both through direct contributions to investigators and to a core research fund and . . . recruit . . . funds from two agencies (UNICEF and Rotary International Foundation) which have not traditionally funded research.[52]

And he believed that the resulting structure would have broad implications:

> This type of dynamic, problem-solving mechanism for addressing research needs appears to offer a unique and potentially highly productive model for addressing problems pertaining to control and/or eradication of other vaccine-preventable disease. In fact, it has been suggested by the Director-General of WHO that if this approach proved workable, its agenda should soon be broadened to embrace other diseases.[53]

His hopes for polio to become a model for other vaccines was again a resurgence of his abandoned desire to change the entire vaccine development system. The audacity of Henderson's polio plans could not have been lost upon Grant—who as head of UNICEF was in a far better position to make things happen on the world scene than a single individual without a powerful international agency backing him up.

JAMES GRANT OF UNICEF RETHINKS RESEARCH

It is also likely that Henderson had such a dramatic impact upon Grant's thinking because Grant had already mentally moved away from UNICEF's traditional antiresearch position as a result of the influence of the Commission on Health Research for Development, headed by John R. Evans (chairman of the Rockefeller Foundation). The "Evans commission" had been formed in 1987 as an independent international initiative with the goal of improving health in the developing world. It was "focused on research in the belief that it [research] has enormous—and, in great part, neglected—power to accomplish that goal."[54] One of the commission's key recommendations, authored by Dr. Lincoln Chen of Harvard, was that multilateral development agencies should raise funding levels for research and that "at least 5 percent of project and program aid for the health sector from development aid agencies should be earmarked for research and research capacity strengthening."[55] That message had been delivered during 1987–88 in a series of private meetings between Chen and Grant. On several occasions, Chen had been invited to present the commission's deliberations to Grant's senior management staff and to dis-

cuss the importance of research. Grant was simultaneously planning for the World Summit for Children that would meet in 1990, and the summit, "Jim [Grant] recognized, had to be backed by a research initiative." Chen and the commission's message was persuasive enough that Grant was the only leader of a large multilateral development agency to accept the recommendation and "take" the 5 percent pledge at the commission's Stockholm meeting in February 1990.[56] It seems reasonable to assume that Grant's desire to dedicate part of UNICEF's funds to research could not be put into action until he had a specific project in mind—and Henderson provided the inspiration for that.

Thus, as a result of the powerful argument that Henderson made for polio and other vaccine research, and the pledge that Jim Grant had made to the Evans commission, Grant took Henderson's proposal for a "Manhattan-Type Project" for Polio, and converted it into a general call for a "Manhattan Project" for vaccines. However, in this incarnation the "Manhattan Project" would have as its ultimate aim the creation of a single multi-antigen vaccine given near birth and providing immunity for life—a decided divergence from Henderson's original, broad-focused goal.

To get things moving Grant asked one of his staff, Dr. Terrell Hill, to write a research proposal for submission to the UNICEF executive board at its April 1990 meeting. The proposal was a sweeping statement of the importance for UNICEF of supporting vaccine research.

The resulting document reviewed the major drop in child mortality over the previous decade as the result of increased coverage of the six EPI vaccines (those for diphtheria, pertussis, tetanus [DPT], polio, measles, and tuberculosis). It went on to say that the World Health Assembly had adopted as its goals the eradication of polio by the year 2000, the elimination of neonatal tetanus by 1995, and the reduction of measles mortality by 90–95 percent by the year 2000. However, the achievement of these goals was in doubt due to problems in the current vaccines: the vaccines were not totally effective, were often given to late to be potent, often lacked the ability to tolerate tropical heat, and required multiple shots that necessitated complex delivery systems.[57]

The UNICEF document went on to make a number of specific recommendations:

> it is proposed that UNICEF secure financial support for the WHO Programme for Vaccine Development and Transdisease Vaccinology in collaboration with other agencies. This support will be focused upon further development of (in order of priority) (a) polio vaccine that is heat stable, offers a better immune response and . . . [is] safer . . . ; (b) a tetanus toxoid vaccine that will offer timed release, thus requiring only one injection; and (c) a safer pertussis [vaccine] . . . and a DPT vaccine that [requires] . . . only a single injection.[58]

The research would be done by WHO's Programme for Vaccine Development in cooperation with Johns Hopkins University. As part of the effort the program would involve scientists and laboratories around the world. To achieve the immediate goal, Jim Grant recommended that the executive board approve $15 million in the period 1990–94.[59]

The document concluded with the announcement that a "broader proposal requiring greater resources is being developed for the presentation at the World Summit for Children in September 1990," and that "the programme is expected to facilitate the eventual creation of a single-dose, multi-antigen vaccine that can be administered very early in life."[60] What one can clearly see in this promise of a larger proposal for the World Summit for Children is Jim Grant's plan to move beyond D. A. Henderson's "narrowly focused" research agenda toward William Foege's (Bellagio II) magic bullet. (It is probable that Grant thought that Henderson would be supportive of that expansion.)

THE UNICEF BOARD IS NEGATIVE TO RESEARCH

When the UNICEF executive board met, it unexpectedly rejected the proposal, despite the fact that Grant verbally informed its members that he had publicly pledged to the Evans commission that he would dedicate 5 percent of his budget to research.[61] The board's action left Grant and his staff in a highly embarrassing position.

An insider view of what motivated at least one delegation's rebuff of the UNICEF document can be obtained from the internal memoranda of the U.S. delegation to the UNICEF board. The American position was that the proposal in its present form was unacceptable, and needed to be significantly modified. There were a number of problems with it: First, it raised the fundamental question of "whether UNICEF should become involved in support of biomedical research" or whether it's "resources might be better spent in areas more traditional for UNICEF."[62] The U.S. delegation felt that the change in direction that the executive director suggested needed to be thought through very carefully:

> The proposal goes to the heart of an issue that has come up at all recent Board meetings; i.e., what kind of UNICEF does the Board want to have? In general, the Board has held that UNICEF should be a field-oriented organization which supports programs at the country level to provide direct and immediate benefits to children and women.[63]

There was increasing pressure to create specific funds for special interests and this was simply the latest such request. Second, the United States possessed a number of agencies and programs that engaged in research, as did the World Health Organization and others. The fact